EFFECT OF AEROBIC EXERCISE TRAINING ON ESTIMATED HEPATIC BLOOD FLOW AND PLASMA PROPRANOLOL CONCENTRATION AFTER ORAL ADMINISTRATION IN YOUNG AND ELDERLY ADULTS

BY

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This work is dedicated to my family for all their endless patience, love and support over the last 5 years.

Thank you for always being there for me.

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Abstract of Dissertation Presented to the Graduate School
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EFFECT OF AEROBIC EXERCISE TRAINING ON ESTIMATED HEPATIC BLOOD FLOW AND PLASMA PROPRANOLOL CONCENTRATION AFTER ORAL ADMINISTRATION IN YOUNG AND ELDERLY ADULTS

By

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Major Department: Exercise and Sport Sciences

To evaluate the effect of 4 months of endurance training on estimated hepatic blood flow (EHBF) and oral propranolol pharmacokinetics, 23 young (Y) (30±5 years) and 20 elderly (E) (67±5 years) adults were randomly assigned to endurance training (Y: n=12; E: n=10) or nonexercising control (Y: n=11; E: n=10) groups. Training consisted of treadmill walking and/or stairclimbing 3 times per week. EHBF and plasma propranolol concentrations following a single dose of 80 mg of oral propranolol were measured, before and after 4 months of training, based on blood samples taken sequentially during supine rest. Blood samples were quantified using indocyanine green and HPLC technology, respectively.

Training increased maximal oxygen uptake (VO_2max) (Y:12.5±3.6%; E:13.6±5.5%) and plasma volume (PV) (Y:15.2±1.6%; E:12.6±2.2%) in both the young and elderly exercisers, relative to controls. Relative increases in VO_2max and PV for the young and elderly exercisers did not differ. Initial values of EHBF (Y: 1306±378 ml/min; E: 1073±354 ml/min) and the area under the curve to hour 10 for oral propranolol concentrations (Y: 558±214 ng/ml; E: 658±369 ng/ml) were not different between the young and elderly. After the 4 months a 2x2 factorial analysis of covariance (ANCOVA) found a significant interaction between age and treatment in EHBF. Post-hoc analysis showed that EHBF was not different between the elderly control and training groups. However, adjusted posttraining means for the young control (1126 ml/min) and training (1338 ml/min) groups were significantly different. However, differences were due to the control group decreasing and the training group not changing. No differences were found in the pharmacokinetics of oral propranolol after 4 months of training in either group.

The results show that 1) young and elderly adults increase VO_2max and PV to the same relative extent when given a similar training stimulus; 2) at baseline, healthy elderly adults do not differ in EHBF or oral propranolol pharmacokinetics when compared to the young; 3) 4 months of exercise training does not increase EHBF in young or elderly adults; and 4) 4 months of exercise training does not change the pharmacokinetics of oral propranolol in young or elderly adults.

CHAPTER 1
INTRODUCTION

The fastest growing segment of the population in the United States today is the elderly, i.e., those who reach or pass the age of 65 (Brody, Brock, & Williams, 1987). There are now nearly 30 million elderly people in the United States, a figure that will climb to 64.6 million or 21% of the population by the year 2030 (U.S. Bureau of the Census, 1983). This progressive increase in the age of the population has produced an increasing interest in medical problems in the elderly.

Measurements of functional capacity of most of the organ systems show a linear decline beginning in young adulthood and continuing throughout life (Robinson, 1938; Astrand, 1960; Hodgson & Buskirk, 1977). Aging itself as well as decreased physical activity associated with aging may cause alterations in the function of these organ systems in the absence of any well-defined disease. One vital organ that changes with age is the liver. The liver loses about 40-50% of its functional capacity between the ages of 30 and 70 years (Smith, 1981). The liver is important in total body metabolism and is involved in the detoxification of various drugs taken to fight disease or to help maintain body function. When the liver does not function at the fullest capacity, although there is ample functional reserve, there is increased potential for drug toxicity, which can lead to further medical complications.

One of the reasons that liver function may change in the elderly is due to a decrease in liver blood flow. Studies using ICG to evaluate liver blood flow have shown liver blood flow to decline in the older adult (Wood, Vestal, Wilkinson, Branch, & Shand, 1979; Woodhouse & Wynne, 1988; Wynne, Cope, Mutch, Rawlins, Woodhouse, & James, 1989; Wynne et al, 1990). Wood et al. (1979) showed a significant negative correlation between age and ICG clearance ($p \leq 0.004$). Wynne et al. (1989) measured ICG clearance in 65 healthy volunteers aged 24 to 91 years and showed a decline in apparent liver blood flow of 53% in those over 65 years compared with those under 40 years. After allowing for changes in body weight, a 47% decline in apparent liver blood flow was observed. Furthermore, liver perfusion (liver blood flow per unit of liver volume) also fell, by a factor of 20%.

The pharmacokinetic consequences of the age-related fall in liver blood flow have been examined in several studies (Castleden, Kaye, & Parsons, 1975; Castleden & George, 1979; Greenblatt, Sellers, & Shader, 1982; Rigby, Scott, Hawksworth, & Pertrie, 1985). Surveys have shown that the incidence of adverse drug reactions rises steadily with age (Hurwitz, 1969). In many instances, this apparent increase can be accounted for by increased drug usage (Woodhouse, Mortimer, & Wiholm, 1986). However, it does appear that the elderly are at risk for developing dose-dependent adverse drug reactions. Part of the explanation for this phenomenon may be increased sensitivity to drugs, as well as the decrease in systemic elimination of drugs, leading to higher blood concentrations and hence adverse effects (Greenblatt et al., 1982). The decline in liver blood flow with aging may be a major reason for age-related adverse drug reactions.

Propranolol is an example of a drug whose metabolic fate is determined solely by the liver. Propranolol is one of the oldest beta-adrenoreceptor antagonists, having a vast use in the treatment of arterial hypertension, angina pectoris and some cardiac arrhythmias. Its metabolic fate is extensively hepatic oxidation, with only negligible amounts being excreted in the unchanged form (Shand, Nuckolis, & Oates, 1970). The factors determining the circulating concentrations of propranolol are somewhat complex and depend on both the route and duration of drug administration (Wilkinson & Shand, 1975; Wood, Vestal, Wilkinson, Branch, & Shand, 1978; George, 1979; Kornhauser, Routledge & Shand, 1979). After intravenous injection, the hepatic clearance of a highly extracted drug such as propranolol is greatly dependent on liver blood flow. However, after oral administration the apparent clearance of propranolol, in theory, is not altered to a large extent by liver blood flow, provided that the hepatic vascular anatomy is normal (Wilkinson & Shand, 1975; Kornhauser et al., 1978; George, 1979; Routledge & Shand, 1979;).

Propranolol is lipid soluble and is rapidly and completely absorbed from the gastrointestinal tract. It, however, undergoes extensive metabolism on the first-pass through the liver and as a consequence has a bioavailability of about 30% (Johnsson & Regardh, 1976). The bioavailability of propranolol is dose dependent so a progressively higher fraction of the dose reaches systemic circulation as the dose is increased (Shand & Rangno, 1972). Bioavailability is a percentage term indicating how much of a drug is available for pharmacodynamic action. Evans, Wilkson, and Shand (1973b) explained this phenomenon as being due to saturation of a high affinity, low capacity system for removing the beta-blocker, probably making up the microsomal cytochromal P450 enzyme system. The clearance of oral propranolol, therefore, is greatly dependent on the activity of the hepatic drug metabolizing enzymes in individuals with normal liver function (Routledge & Shand, 1979).

The bioavailability of propranolol is also affected by proteins in the plasma (Evans, Nies, & Shand, 1973a). The major proteins that bind propranolol are serum albumin and alpha$_1$ acid glycoprotein. The degree of plasma binding is one determinant of the distribution of propranolol into tissues. Thus, bioavailability increases as plasma binding increases (Evans et al., 1973a).

Studies comparing young and elderly adults have found differences in the pharmacokinetic properties of propranolol (Castleden et al., 1975; Castleden & George, 1979; Vestal, Wood, Branch, Shand, & Wilkinson, 1979; Regardh, 1982; Rigby et al., 1985;). When compared to the young, blood concentrations of propranolol in the elderly have been found to be three to four times higher (Castleden et al., 1975; Castleden & George, 1979; Regardh, 1982), whole body clearance of propranolol has been found to decrease by 50% (Rigby et al., 1985), and half-life has been found to increase from 4.2 to 5.1 hours (Vestal et al., 1979). Geokas and Haverback (1969) have suggested that certain drugs such as propranolol are metabolized more slowly due to age-related changes in drug-metabolizing enzymes. Although the dangers from these increased blood levels of propranolol in the elderly are minor, other drugs that have a significant presystemic elimination during their passage from the gut to the systemic circulation may require a considerable reduction in dose compared to younger individuals.

Some of the reasons for the age-related decline in liver blood flow and age-related differences in concentrations of propranolol may be the age-related decrease in resting cardiac output (Brandfonbrener, Landowne, & Shock, 1955), decreased plasma volume (Stamford, 1988), and increased resistance to blood flow due to either stiffening and/or fatty deposits on the walls of the vessels (Smith, 1981). Clearly the genetic components of age control the overall length of life and the ability of the organ systems to maintain function, but the quality of life is controlled by how people interact with their environment. Current research suggests that 50% of the decline in functional capacity frequently attributed to physiological aging is disuse atrophy resulting from inactivity in an industrialized world (Smith, 1981). Exercise training in middle-aged and older adults has been reported to produce substantial improvements in functional capacity (Stamford, 1988; Pollock and Wilmore, 1990;). Some of these improvements include increases in maximal oxygen uptake (VO_2max) (Adams & deVries, 1973; Pollock et al., 1976; Sidney & Shepard, 1976; Badenhop, Cleary, Schal, Fox, & Bartels, 1983), blood volume (Convertino, 1991; Fellman, 1992), hemoglobin (Convertino, 1991; Fellman, 1992), strength (Moritani & deVries, 1981) and decreases in blood pressure (Seals & Hagberg, 1984; Hagberg & Seals, 1986), percent body fat (Cooper, Pollock, Martin, White, Linnerud, & Jackson, 1976), resting heart rate (Adams & deVries, 1973; Sidney & Shepard, 1976; Seals, Hagberg, Hurley, Ehsani, & Holloszy, 1984) and plasma lipid levels (Wood & Haskell, 1979; Haskell, 1986). Much attention is now being focused on the interactions between physical conditioning and the physiological changes that are associated with the aging process. Whether exercise training in man can increase resting liver blood flow and alter drug pharmacokinetics is unknown. If liver blood flow and metabolism of drugs can be increased by regularly performed endurance training, then many problems associated with decreases in liver function and metabolism may be reduced. Therefore, alterations in drug dosing may be necessary as a result of changes in hepatic blood flow.

Purpose of the Study

The purpose of the study was to evaluate the effects of 16 weeks of aerobic training on estimated hepatic blood flow (HBF) and concentrations of plasma propranolol after a single oral dose in older and younger adults.

Research Hypothesis

The hypothesis tested was that 16 weeks of aerobic training increases resting liver blood flow in younger and older adults. It is also hypothesized that the plasma concentrations of propranolol after oral ingestion are lower after 16 weeks of aerobic training in both younger and older adults.

Justification

The liver performs many functions that are vital to the health of the organism. The liver is essential in regulating metabolism, in synthesizing certain proteins, in serving as a storage site for certain vitamins and iron, in degrading certain hormones, and inactivating and excreting certain drugs and toxins (Berne & Levy, 1988). The liver is dependent on blood flow in receiving these products and transporting by-products to other organ systems of the body. A decline in liver blood flow with aging and inactivity may be a major component of age-related alterations in the liver and the ability of the liver to function. If an exercise program can increase liver blood flow, age-related decrements would be reduced and the liver would be able to work more efficiently. To date no data are available on the effect of exercise training on hepatic blood flow in young or elderly adults.

Propranolol was selected as a model drug because it undergoes extensive first-pass extraction and is commonly prescribed in medical practice, and estimation of its concentration in plasma is relatively simple. There is a growing realization that aerobic activity can have a major impact on health, not only in healthy adults, but also in patients suffering from a wide range of diseases. This could mean that an increased number of individuals is exercising while on medication, and the effects of chronic exercise may influence the ability of the liver to metabolize different types of drugs. From the data obtained in this study we will learn if aerobic exercise training can cause hepatic metabolism to become more efficient in eliminating propranolol. Consideration then would be needed for the prescription of drug therapy to older adults involved in an aerobic exercise program.

Assumptions

1. All laboratory equipment will yield accurate measurements over the course of repeated testing.

2. Subjects will follow instructions given to them regarding food, drink, and drug intake prior to testing.

3. Subjects will follow instructions given to them regarding the maintenance of current lifestyle (e.g., diet and exercise) outside of the prescribed program.

Delimitations

The delimitations for this study were as follows:

1. Fifty-five volunteer subjects from the Gainesville area and Alachua County, Florida served as subjects. Twenty-nine of the subjects were between the ages of 19 and 40 and twenty-six were between the ages of 60 and 80 years of age.

2. The subjects were free from exercise-limiting disease with no previous involvement in any type of regular exercise program

for the last 12 months (see criteria for exclusion in methodology).

3. During the study the subjects did not change their diet in any way or start any additional exercise programs outside the laboratory.

4. Exercise was delimited to 16 weeks of aerobic training on motorized treadmills and stairclimbing machines.

5. The drug model was delimited to a single dose of 80 mg of propranolol.

Limitations

The major limiting factors of this study were as follows:

1. When dealing with human subjects it is often very hard to choose a representative sample from the universe of interest. Subjects were recruited from the Gainesville, FL area. Subjects were from the upper middle class since these individuals usually have the means, time, and interest to be involved in a study of this duration. The subjects of this study were volunteers and therefore were highly motivated and looked for exercise benefits. For these reasons the volunteers from this study may not be true representations of the entire universe.

2. Bias will also exist in this sample. There is geographical bias due to subjects being only from the Gainesville, FL area. There is also a socioeconomic bias. Increase motivation may also lead to bias in this study. The biases of gender and age were controlled for by the proper inclusion of subjects in the study and randomization process.

3. Since subjects are healthy and are highly motivated, the response variables may be higher than one would normally expect if an individual could have been randomly chosen from the universe. Conclusions from this study must take into account the type of individual agreeing to participate in the study and living in this particular area.

4. Diet, sleep, and other out-of-laboratory activities are not controlled. Subjects were, however, advised not to change their lifestyle during the 5 month study.

Definition of Terms

Clearance--the efficiency of an organ to irreversibly remove a drug from the perfusing plasma; the volume of plasma that is completely freed of drug expressed as a volume per unit of time (Rowland & Tozer, 1989).

First-pass effect--a drug that is absorbed from the intestine passes through the liver and is metabolized in the liver and is excreted in the bile; some of the active drug will be inactivated or diverted before it reaches the general circulation; drug removal after absorption (Rowland & Tozer, 1989).

Half-life ($t_{1/2}$)--the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50% (Rowland & Tozer, 1989).

Indocyanine Green (ICG)--a tricarbocyanine dye first developed for use in color emulsion (Caesar et al., 1961).

Maximal Heart Rate Reserve (%HRRmax)--percent difference between resting and maximal heart rate at which exercise is performed (Pollock & Wilmore, 1990).

Pharmacokinetics--the time course of drugs and their metabolites in various tissues of the body (Peck, Conner, & Murphy, 1989). Holford and Sheiner (1981) suggest that pharmacokinetics be considered "what the body does to the drug."

Propranolol--a beta-adrenoreceptor antagonist that is used in the treatment of arterial hypertension, angina pectoris, and some cardiac arrhythmias (Pollock et al., 1991).

Rating of Perceived Exertion (RPE)--a 15-point category scale ranging from 6 to 20 with a descriptive verbal anchor at every odd number (Borg, 1982).

CHAPTER 2
LITERATURE REVIEW

Liver Function

The liver performs many functions that are vital to the health of the organism. The liver is essential in regulating the secretion of bile; in regulating metabolism of carbohydrates, lipids, and proteins; in synthesizing proteins as well as plasma lipoproteins; in serving as a storage site for certain vitamins and iron; in degrading and excreting hormones such as norepinephrine and epinephrine; and inactivating and excreting certain drugs and toxins. The liver, therefore, depends on blood flow to receive products and transport by-products to other organ systems of the body (Berne & Levy, 1988).

In the human adult, the total splanchnic blood flow is about 1500 ml/min, which is approximately 25% of the cardiac output at rest. This blood flow is derived from two sources, the portal vein and the hepatic artery. The splanchnic vasculature has some unique characteristics in that the portal circulation is coupled with that of the gastrointestinal (GI) tract in series and with the hepatic artery in parallel. The arteries to the various splanchnic organs of the GI tract, the spleen, and the pancreas have many interconnecting branches. The portal blood supply is controlled by various factors that determine flow through the GI tract and spleen. In contrast, hepatic artery blood flow is principally controlled by local metabolism. About 70-80% of the liver blood flow is from the portal vein and about 20-30%

travels via the hepatic artery. Since the portal venous blood has already passed through the GI capillary bed, most of the oxygen has already been extracted. The hepatic artery then delivers the remaining one fourth of the blood, which is fully saturated with oxygen (Berne & Levy, 1988). Upon entering the liver, blood flows to the veins and arteries of the portal triads, enters the sinusoidal spaces of the liver, and exits via the central hepatic vein. Transfer of drugs, for example, between the blood and the hepatocyte occurs within the sinusoids. The metabolism or excretion of unchanged drug into the biliary system occurs at the level of the hepatocyte.

The affinity of the liver to extract drugs from the blood depends on the drug's physical and chemical makeup. Generally, drugs are characterized as being of high or low affinity for extraction by the liver. Drugs with high hepatic extraction tend to be less available to systemic circulation and have a high systemic clearance. On the other hand, drugs with low affinity for hepatic extraction tend to be more available to the systemic circulation and have a low systemic clearance. The efficiency of the liver in removing a drug from the bloodstream is referred to as the extraction ratio (E). This is the fraction of drug that is removed during one pass through the liver. The value of E ranges from 0 to 1, where high extraction is closer to one and low extraction is closer to 0 (Rowland & Tozer, 1989).

For a drug that is only eliminated by the liver, systemic clearance is dependent on (1) the liver's innate ability to irreversibly remove the unbound drug from the plasma; (2) the fraction of drug unbound or free drug in the blood; and (3) hepatic blood flow (HBF). A mathematical model explains the relationship between systemic clearance and the above three conditions (Rowland & Tozer, 1989):

$CL_H = Q_H F_p CL_i / Q_H + F_p CL_i$

where

CL_H = hepatic drug clearance

F_p = free fraction of drug in plasma

CL_i = intrinsic clearance

Q_H = hepatic blood flow

In a normal 70-kg man, total HBF (Q_H) is approximately 1500 ml/min. Obviously, changes in HBF would change the rate of drug delivery to the liver and impact liver clearance (CL_H). However, the magnitude of impact would depend on the liver's ability to remove or extract the drug and whether the drug is free or unbound (F_p). Only the free or unbound drug is available to the hepatocytes to be metabolized. Intrinsic clearance (CL_i) represents the liver's innate ability to clear unbound drug from intracellular water. Changes in intrinsic clearance have a profound effect on hepatic clearance. However, as with hepatic clearance, the extent and magnitude of an effect would depend on the extraction characteristics of the specific drug (Rowland & Tozer, 1989).

In high intrinsic cleared drugs, intrinsic clearance is much greater than HBF. Therefore, HBF becomes insignificant when compared to the intrinsic clearance, or in other words, hepatic clearance equals HBF.

$CL_H = Q_H F_p CL_i / Q_H + F_p CL_i$ this will approach

$Q_H F_p CL_i / F_p CL_i = Q_H$

Here hepatic clearance is essentially a reflection of the delivery rate of the drug to the liver. Thus, blood flow changes will produce similar changes in the hepatic clearance. Following intravenous administration the hepatic clearance of highly extracted drugs is dependent on HBF and independent of intrinsic clearance and free fraction of drug in plasma (Rowland & Tozer, 1989).

In low intrinsic cleared drugs, HBF is much greater than the drug's intrinsic clearance.

$CL_H = Q_H F_p CL_i / Q_H + F_p CL_i$ this will approach

$Q_H F_p CL_i / Q_H = F_p Ci$

Therefore, the hepatic clearance of drugs with low extraction ratios is virtually independent of HBF and hepatic clearance becomes a function of intrinsic clearance and free fraction of drug in plasma (Rowland & Tozer, 1989).

An important characteristic of drugs having a high extraction ratio is that in oral administration a significant amount of the drug will be metabolized prior to reaching the systemic circulation. This is referred to as the "first-pass" effect, of which propranolol is the prototype drug. When a drug is given orally the drug is absorbed though the GI tract and taken to the liver by the portal vein prior to entrance into the general circulation via the hepatic vein. This results in the amount of drug reaching the systemic circulation to be considerably less than the dose given. Drugs given intravenously do not undergo the "first-pass" effect and, therefore, much more is available to the systemic circulation (Rowland & Tozer, 1989).

Hepatic Blood Flow

Studies measuring hepatic blood flow (HBF) have used a number of surgical and pharmacokinetic techniques, and consequently a variety of methods of assessment have been developed. Since there is a dual supply of blood to the liver, direct measurements of HBF are difficult and are severely limited in humans by ethical constraints. Therefore, indirect methods have been developed to estimate HBF that employ clearance techniques using flow limited substances.

Bromosulphthalein (BSP) was first described by Bradley et al. (1945), being considered suitable because of its high hepatic extraction. However, BSP was not an ideal model, since BSP had a significant enterohepatic circulation as well as age-related changes in metabolism (Woodhouse & Wynne, 1988). A better model agent used for evaluating liver blood flow is indocyanine green (ICG). Indocyanine green is a tricarbocyanine dye first developed for use in color emulsion (Caesar et al., 1961). Wheeler et al. (1958) showed that following intravenous injection in dogs (1) the ICG dye was bound to albumin; (2) it was rapidly distributed in the circulating plasma; (3) it failed to appear in extravascular fluids; (4) biliary excretion was almost complete; and (5) there was no demonstrable enterohepatic circulation (Wheeler et al., 1958). It was also shown that there were no age-related changes in hepatic extraction ratio in humans, averaging 74% in normal volunteers (Leevy, Mendenhall, Lesko, & Howard, 1962; Grainger, Keeling, Brown, Marigold, & Thompson, 1983; Wynne et al., 1990), as well as no age-related changes in the maximal rate of removal of the dye in aging rodent livers (Kitani et al., 1978).

Ideally, in order to calculate HBF using either of these two dyes, the Fick principle is used and the concentrations of dye entering the liver at steady-state must be known. Therefore, hepatic vein catheterization is required. The direct methods involve extensive procedures and operations and are therefore unsuitable for human pharmacokinetic studies. To avoid invasive procedures, plasma clearance determined after a single injection for estimating HBF has been developed for both BSP (Clarkson, Hardy-Smith, & Richards 1976) and ICG (Grainger et al., 1983).

The uptake of ICG can be estimated by venous sampling over a certain time period at a peripheral vein. The clearance of ICG can be calculated according to a one compartment model by linear regression of the log plasma concentration values. Once the plot is determined the disappearance rate constant (K_e) can be calculated (Ohnhaus, 1979). The equation for estimating HBF is

Estimated HBF = $K_e \times PV / .74(1 - Hct)$

where K_e = the elimination rate constant
PV = plasma volume
Hct = hematocrit

One of the earliest and largest studies of liver size and aging was undertaken by Boyd (1933). Data regarding liver weight were retrospectively collected in 1582 subjects between the ages of 20 and 80 years and dying within 24 hours of acute injury or accident. A fall in liver size of 24% in males and 18% in females was noted between the third and sixth decade of life. Changes were most marked after the sixth decade. Calloway, Foley, and Lagerbloom (1965) also noted a 25% fall in liver weight between the ages of 20 and 70 years. A larger fall was seen in the very old with a decline of 46% between the third and tenth decades.

Most studies investigating the effect of age on human liver size *in vivo* have used ultrasound. Swift, Homeida, Halliwell, and Roberts (1978) measured liver size in 15 volunteers in the third decade and 11 healthy volunteers aged 75 to 86 years. A reduction in estimated liver volume from a mean 1303 ml in the young group to 990 ml in the older group was found, a difference of 24%. Bach, Molholm, Hanson, Kampmann, Rasmussen, and

Skorsted (1981) also showed a 17% decrease in liver volume between the third and ninth decades. Wynne et al. (1989) also examined the relationship between liver size and age of 65 healthy volunteers between the ages of 24 and 91. They found a significant negative correlation with age and liver size whether expressed in absolute terms or in relation to body weight. A 28% fall in liver volume was seen in those over 65 compared with those under 40.

Studies using ICG to evaluate liver blood flow have shown liver blood flow to decline with age (Wood et al., 1979; Woodhouse & Wynne, 1988; Wynne et al., 1989; Wynne et al. 1990). Wood et al. (1979) showed a significant negative correlation between age and ICG clearance ($p \leq 0.004$). Wynne et al. (1989) measured ICG clearance in 66 healthy volunteers aged 24 to 91 years and showed a decline in apparent liver blood flow from 1,717 ml/min to 807 ml/min. This represents a 53% decline in liver blood flow. Values for men and women ranging from 24 to 91 after allowing for changes in body weight showed a 47% decline in apparent liver blood flow, 25.7 ml/min/kg body wt to 13.5 ml/min/kg body wt. Furthermore, liver perfusion (liver blood flow per unit of liver volume) also fell, by a factor of 20%, from 1.18 ml/min to 0.94 ml/min. Absolute values for HBF were lower in women; however, when expressed per unit, body weight values were similar. Mean values and standard deviations for men and women under 40 were 23.4±0.9 ml/min•kg and 24.1±0.5 ml/min•kg, respectively, and over 65 were 16.2±0.6 ml/min•kg and 14.8±0.5 ml/min•kg.

A decline in liver volume and HBF with aging may be a major component of age-related alterations in the liver, leading to the fall in clearance of many drugs whose pharmacokinetics have been found to be altered with age. The significant fall in liver blood flow must be an important contributor to the reduced systemic elimination of drugs by the elderly. This will be of great importance for high and intermediate clearance drugs such as verapamil (Storstein, Larsen, Midtbo, & Saevareid 1984), morphine (Baillie, Bateman, Coates, & Woodhouse, 1989), and propranolol (Castleden & George, 1979), all of which have a significant age-related decrease in the rate of metabolism.

Propranolol

The pharmacokinetic consequences of the age-related fall in liver blood flow has been examined in several studies (Castleden et al., 1975; Castleden & George, 1979; Greenblatt, Sellers, & Shader, 1982; Rigby et al., 1985). Surveys have shown that the incidence of adverse drug reactions rises steadily with age (Hurwitz, 1969). In many instances, this apparent increase can be accounted for by increased drug usage (Woodhouse et al., 1986). However, it does appear that the elderly are at risk for developing dose-dependent drug reactions. Part of the explanation for this phenomenon may be increased sensitivity to drugs, as well as the decrease in systemic elimination of drugs, leading to higher blood concentrations and hence adverse effects (Greenblatt et al., 1982). The decline in liver blood flow with aging may be a major reason for age-related adverse drug reactions. This may explain some of the problems that are associated with drug therapy in the elderly individual.

Propranolol is an example of a drug whose metabolic fate is determined solely by the liver. Propranolol is one of the oldest nonselective beta-adrenoreceptor antagonists, having a vast use in the treatment of arterial hypertension, angina pectoris, some cardiac arrhythmias, migraine headaches, hyperthyroidism, and essential tremors. It specifically competes with beta-adrenergic receptor agonists for available receptor sites. When beta-receptor sites are blocked by propranolol, the chronotropic, inotropic, and vasodilator resonses to beta-adrenergic stimulation are decreased proportionately. Peak effect occurs in one to one and one-half hours. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely among individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration (Gilman, Rall, Nies, & Taylor, 1990)).

Since propranolol has a high affinity for liver extraction, its metabolic fate is extensively by hepatic oxidation, with only negligible amounts being excreted in the unchanged form (Shand et al., 1970). The factors determining the circulating concentrations of propranolol are somewhat complex and depend on both the route and duration of drug administration (Wilkinson & Shand, 1975; Kornhauser et al., 1978; George, 1979; Routledge & Shand, 1979). After intravenous injection, the hepatic clearance of a highly extracted drug such as propranolol is greatly dependent on HBF. However, after oral administration the apparent clearance of propranolol, in theory, is not altered to a large extent by HBF, provided that the hepatic vascular anatomy is normal (George, 1979; Kornhauser et al., 1978; Routledge & Shand, 1979; Wilkinson & Shand, 1975). Routledge and Shand (1979) explain that even with highly extracted drugs, like propranolol, the area under the curve (AUC) after a single oral dose depends more on the activity of the hepatic drug metabolizing enzymes and not on HBF. This occurs because the AUC of an oral dose is determined by presystemic and systemic clearance, and these change in opposite directions when HBF is changed. For example, when flow is reduced, presystemic extraction increases, but the ability of the liver to clear the smaller amounts that reach the systemic circulation is reduced.

Propranolol is lipid soluble and is rapidly and completely absorbed from the GI tract. Because of the extensive metabolism on the first-pass through the liver, the bioavailability is about 30% (Johnsson & Regardh, 1976). The bioavailability of propranolol is dose dependent so a progressively higher fraction of the dose reaches systemic circulation as the dose is increased (Shand & Rangno, 1972). Evans, Wilkson, and Shand (1973b) explained this phenomenon as being due to saturation of a high affinity, low capacity system for removing the beta-blocker, probably making up the microsomal cytochromal P450 enzyme system. The clearance of oral propranolol, therefore, is greatly dependent on the activity of the hepatic drug metabolizing enzymes in individuals with normal liver function (Routledge & Shand, 1979).

Protein Binding

The bioavailability of propranolol is also affected by proteins in the plasma (Evans et al., 1973a). Propranolol is highly bound (85 to 96%) to two major proteins, serum albumin and alpha$_1$ acid glycoprotein (AAG). Alpha$_1$ acid glycoprotein is responsible for 75% of binding of propranolol in plasma at therapeutic concentrations (Routledge & Shand, 1979). Alpha$_1$ acid glycoprotein is an acute-phase protein, which is raised in inflammatory conditions. As a consequence of this, increased protein binding has been reported for propranolol in association with disease-induced elevations of AAG (Piafsky, Borga, Odar-Cederlof, Johansson, & Sjoqvist, 1978). This effect is probably one of the reasons that a reported sevenfold increase in plasma levels of propranolol was seen in a group of patients with active inflammatory disease (Schneider, Bishop, Kendall, & Quarterman, 1981). The amount of protein binding is essential for the relationship between plasma concentrations and its effects. Only the unbound fraction of the drug is considered effective; however, the plasma levels are usually reported as the sum of bound and free drug (Regardh, 1982). Therefore, the degree of plasma binding is one determinant of the distribution of propranolol into tissues and may affect hepatic clearance. Thus, bioavailability increases as plasma binding decreases (Evans et al., 1973a).

Effect of Aging on Propranolol Concentrations

With advancing age physiological changes occur in man that contribute to changes in drug absorption and disposition depending on their pharmacokinetic characteristics. The age-related physiological changes include reductions in lean body mass, total body water, serum albumin concentration, liver mass, cardiac output, liver blood flow, renal plasma flow, and glomerular filtration rate (Regardh, 1982). However the rate and the degree of these age-related reductions can be very small or large depending on the genetic makeup, health, and fitness of the elderly individual.

Absorption. For most drugs, including beta-blockers, the rate and extent of absorption is determined by passive diffusion during contact with the vast surface area available for absorption in the proximal bowel. Beta-blockers are lipid soluble and are completely absorbed from the GI tract. There is no evidence to suggest that drug absorption is impaired in old age (Greenblatt et al., 1982).

Distribution and protein binding. Drug distribution in old people may be altered by changes in body composition and changes in plasma proteins to which drugs are bound. Not only do old people generally loss mass, but also their proportion of fat to muscle and water increases, thus enlarging the volume of distribution of lipid soluble drugs (Macklon, Barton, James, & Rawlins, 1980).

Plasma albumin concentration has been shown to decline 10-20% with increasing age (Hayes, Langman, & Short, 1975a; Hayes, Langman, & Short, 1975b; Wallace & Whiting, 1976; Greenblatt, 1979; Dybkaer, Lauritzen, & Krakauer, 1981). Rigby et al. (1985) showed that serum albumin concentration was low in the elderly compared to the young but that there were no significant differences in protein binding of propranolol. A recent report, however, indicates that in healthy males, serum albumin level declines at a rate of 0.54 g/L per decade, and that hypoalbuminia is not a consequence of normal aging (Campion, deLaby, & Glynn, 1988). However, disease, frailty, and immobility can exert a significant influence on serum albumin levels in older adults (MacLennan, Martin, & Mason, 1977). Castleden and George (1979) found no differences in plasma protein concentrations in their elderly and young subjects and concluded that plasma binding of propranolol was likely to be similar between the two groups.

Data are also conflicting concerning the association between age and serum AAG (Durnas, Loi, & Cusack, 1990). Most of the data on serum AAG has been observed with elderly individuals who have been ill (Frishman, 1988). If AAG does increase with age in healthy individuals it may offset the change, if any, in albumin. Increased levels of AAG without reductions in albumin concentrations could theoretically reduce the fraction of propranolol available for binding to receptor sites, thus necessitating higher doses of propranolol for effective treatment.

Metabolism. Geokas and Haverback (1969) have suggested that there are age-related changes in drug-metabolizing enzymes for certain drugs, such as propranolol. Although the dangers from these increased blood levels of propranolol in the elderly are minor, other drugs that may have similar properties, such as significant presystemic elimination during their passage from the gut to the systemic circulation, may require a considerable reduction in dose compared to younger individuals.

Pharmacokinetics. Studies comparing young and elderly adults have found differences in the pharmacokinetic properties of propranolol (Castleden et al., 1975; Castleden & George, 1979; Vestal et al., 1979; Regardh, 1982). Castleden et al. (1975) were the first to show that higher plasma propranolol concentrations were achieved in elderly compared with young adults after a single 40 mg oral dose. At all sampling times during a 10 hour period the elderly (77±2 yrs) had higher concentrations than the young (27±2 yrs). During hour 2 the highest concentration occurred for both young and elderly individuals. During the mean peak for the elderly propranolol concentration was 111 ng/ml, which was more than four times the comparable value in the young subjects (27 ng/ml). Castleden et al. (1975) suggested that the reason the elderly subjects had a greater concentration of propranolol was due to subjects having a substantially reduced first-pass effect. Castleden and George (1979) also found concentrations of propranolol to be higher in the elderly (110 ng/ml) than the young (48 ng/ml) after a single oral dose of 40 mg. Castleden and George (1979) found that the half-lives were similar in the young and old after oral therapy, but the half-life in the elderly (254±52 min) after i.v. therapy (0.15 mg/kg) was longer than the young (152±10 min) subjects. Thus, clearance in the elderly was significantly lower than in the young at 7.8±1.3 ml/kg•min compared with 13.2±1.4 ml/kg•min. Castleden and George (1979) concluded that the observed differences between the two groups is that the rate of elimination was decreased in the elderly by both HBF and first-pass extraction. Vestal et al. (1979) gave 80 mg of propranolol every 8 hr for 2 days to 27 men aged 21 to 73 yr. They found the older subjects had levels up to twice those of the younger subjects, and concentrations were different at all times except at 120 min.

However, a study done by Rigby et al. (1985) found no significant differences in clearance (Y=4518±932 ml/min; E=1982±431 ml/min), AUC (Y=376±85 mg/ml•hr; E=787±145 mg/ml•hr), and terminal phase half-life (Y=3.0±0.4 hr; E=4.7±0.8 hr) of propranolol in healthy elderly (n=6; range 66-72 yr) and young (n=6; range 23-33 yr) adults, although the differences between the age groups looks large. One of the reasons that significance may not have been achieved in the above study could be the small sample size combined with the large variability among the subjects. These results are in conflict to Castleden and coworkers (1975; 1979). Rigby et al. (1985) suggested the difference seen in their study may be due to subjects being healthy, fit, and active whereas Castleden's subjects were older (78±3) and taken from long-stay geriatric wards. However, there were no quantitative measurements given on parameters of health and fitness in either study. If health and fitness levels do play a role in the concentration of propranolol, then research is needed that quantitatively addresses the issue of fitness and health with propranolol therapy.

Exercise, Hepatic Blood Flow, and Propranolol

Some of the reasons for the age-related decline in liver blood flow and age-related differences in concentrations of propranolol may be the age-related decrease in resting cardiac output (Brandfonbrener et al., 1955), decreased plasma volume (Stamford, 1988), increased resistance to blood flow due to stiffening and/or fatty deposits on the walls of the vessels (Smith, 1981), and a decrease in metabolizing enzymes (Geokas & Haverback, 1969; Castleden et al., 1975; Castleden and George, 1979). Clearly the genetic components of age control the overall length of life and the ability of the organ systems to maintain function, but the quality of life is controlled by how a person interacts with his environment. Current research suggests that 50% of the decline in functional capacity frequently attributed to physiological aging is disuse atrophy resulting from inactivity in an industrialized world (Smith, 1981).

Acute Exercise and Pharmacokinetics

The increasing popularity of sporting events, even for people on drug treatment, has raised the question of the interaction between exercise and pharmacokinetics. During acute exercise, a subject's readjustment of his circulation is closely related to the intensity of activity. With progressive increments in exercise intensity the blood flow to active muscles is gradually increased by vasodilation and cardiac output, while the flow to splanchnic (including the liver), renal, and to inactive muscles, is progressively reduced by vasoconstriction (Rowell, 1974).

In order for exercise to alter the pattern of drug metabolism, the drug has to meet certain criteria. If it has a high hepatic clearance, a small volume of distribution, and a short half-life, exercise will decrease clearance of the drug (Ylitalo, 1991). Exercise reduces HBF so less drug is delivered to the liver for metabolism. Rowell (1974) has reported that the half-life of ICG is progressively prolonged with the duration of exercise, indicating the concomitant reduction in HBF. He measured a reduction in HBF of 60% in exercising subjects. Schwartz, Sidell, and Cucinell (1974) believe that liver plasma flow is the major determinant in the disposition of rapidly eliminated compounds such as ICG. Sweeney (1981) has shown that intravenous infusions of lidocaine, a highly cleared drug, produce plasma concentrations that are increased twofold by an hour of strenuous exercise. Exercise induced reduction in HBF may explain the prolongation of the half-life of glyceryl trinitrate, and the increase of serum concentrations of other highly cleared drugs such as propranolol and acebutolol during strenous cycle pedalling for 45-60 min (Henry, Illopoulou, Kaye, Sankey, & Turner, 1981; Kendrick, Cristal, & Lowenthal, 1987; Weber et al., 1987). In contrast, although ICG was reduced in eight healthy subjects exercising on an ergometer for seven hours, the half-life of propranolol was unexpectedly shortened (Arends, Bohm, van Kemenade, Rahn, & van Baak, 1986). In that study the first-pass metabolism of propranolol was probably increased, explaining the reduced bioavailability of the drug in the exercising subjects.

Physical Fitness and Pharmacokinetics

Data are limited on whether the effect of regular exercise on drug metabolism at rest can be changed. Boel, Anderson, Rasmussen, Hansen, and Dossing (1984) believe that improved physical fitness can increase the hepatic elimination of low clearance drugs such as antipyrine and possibly aminopyrine. A longitudinal study done by Broderman, Porter, and Lowenthal (1990) examined antipyrine clearance before and after 6 weeks of aerobic training. No differences were found in the AUC and in the clearance of antipyrine. A study done by Ducry, Howald, Zysset, and Bircher (1979) found that there were no differences between well-trained long distance runners and untrained individuals in hepatic galactokinase activity, liver blood flow, and microsomal metabolism of aminopyrine. The lack of differences in liver function related to physical training may be due to methodological limitations of this study. Subjects were not used as their own controls, instead two independent groups were used. Consequently, individual variation may have obscured minor differences due to training. A longitudinal study might have found different results. The study did find the elimination rate constant for ICG (k_e) to be somewhat lower for the trained subjects (18.43 ± 2.94) than the untrained (20.5 ± 1.22), although the difference was not significant.

General Training Adaptations to Exercise at Rest

Although resting data are lacking on exercise training and liver function, it would seem logical that changes in plasma volume, cardiac output via increases in stroke volume, and peripheral resistance would influence blood flow to the liver and ultimately affect concentrations of propranolol. Below is a brief review of some of the general adaptations of chronic exercise at rest that may effect changes in HBF. Also included are some animal studies that suggest endurance exercise training may increase the activity of the metabolizing enzymes in the liver.

Plasma volume. Increases in HBF may be due to increases in plasma volume with exercise. As early as the late 1940s, it was found that an active person had an elevated plasma volume that was attributed to physical training (Kjellberg, Rudhe, & Sjostrand, 1949). Plasma volume expansion usually occurs with acute endurance exercise and endurance training (Oscai, Williams, & Hertig, 1968; Convertino, Brock, Keil, Bernauer, & Greenleaf, 1980a; Convertino, Greenleaf, & Bernauer, 1980b; Convertino, Keil, & Greenleaf, 1983; Convertino, Montgomery, & Greenleaf, 1984; Convertino, 1991; Allen, Tully, & Bieling, 1992). In most cases, the increase in plasma volume is associated with a decrease in hematocrit (Hct) and hemoglobin (Hb) concentrations without changes in red cell mass (Oscai et al., 1968; Convertino et al., 1980a; Allen et al., 1992).

Plasma volume expansion has been shown to be an early adaptation to almost any degree of endurance exercise, and the plasma volume increase is correlated with the intensity of exercise. Increases of 5%, 10%, 15%, and 20%, respectively, have been reported for moderate exercise, military basic training, a 20-day road race, and elite distance running (Bell & Cowan, 1978; Eichner, 1986; Convertino, 1991; Allen et al., 1992).

Data suggest that the hypervolemic response to training is similar between men and women (Akgun, Tartaroglu, Durusoy, & Kocaturk, 1974; Fortney & Senay, 1979), although the effect of age on hypervolemia is not well defined. Few studies have documented plasma volume responses to training in the elderly. Resting plasma volume does not appear to change with age up to 40 (Chien, Usami, Simmons, McAllister, & Gregersen, 1966), but cross-sectional and longitudinal data are lacking. Convertino et al. (1980a) hypothesized that training-induced hypervolemia might be less in older individuals due to a reduction in physical working capacity. However, since training intensity expressed as a percentage of VO$_2$max appears to be a potent stimulus for plasma volume expansion, the relative hypervolemia induced by training the elderly might be equal to that of younger individuals training at the same relative intensity. Unpublished data by Carroll (1992) showed an increase in plasma volume of 9.5% of elderly individuals who underwent a six month aerobic training program. The relative increase in plasma volume was similar to the 9-12% increase seen in younger individuals (Convertino et al., 1980a; Convertino et al., 1980b; Convertino, 1991).

Cardiac output. Cardiac output at rest has been shown to decrease after an endurance training program (Saltin, Blomquist, Mitchell, Johnson, Wildenthal, & Chapman, 1968; Clausen, Klausen, Rasmussen, & Trap-Jensen, 1973) while other studies have shown no significant changes (Ekblom, Astrand, Saltin, Stenberg, & Wallstrom, 1968; Kilbom & Astrand, 1971). Cardiac output is a function of heart rate and stroke volume. Thus the reason cardiac output may decrease or stay relatively the same with endurance training is due to a greater reduction in heart rate than a rise in stroke volume. With endurance training, resting heart rate has been shown to decrease (Saltin et al., 1968; Pollock, Miller, Janeway, Linnerud, Robertson, & Valentino, 1971; Clausen et al., 1973; Pollock et al., 1976; Hagberg, Montain, Martin, & Ehsani, 1989; Seals & Chase, 1989). This decrease may be related to training-induced hypervolemia (Fortney, Wenger, Bove, & Nadel, 1983), decreased sympathetic nervous system activity (Katona, McLean, Dighton, & Guz, 1982; Bjorntorp, 1987), and/or increased parasympathetic tone (Barney, Ebert, Groban, & Smith, 1985; Kenney, 1985; Seals & Chase, 1989). Stroke volume may not change at rest (Ekblom et al., 1968) or increase (Hartley et al., 1969; Convertino, 1991) with physical training in young and middle-aged persons. Increases may be related again to hypervolemia and elevated central venous pressure (Convertino, Mack, & Nadel, 1991) or to changes in cardiac loading conditions such as decreased peripheral resistance and increased left ventricular end diastolic volume (Ehsani, 1987).

In older adults the data on resting cardiac output are limited. In the healthy elderly subjects the resting heart rate does not appear to vary with age (Strandell, 1964). There is, however, a gradual decrease in stroke volume that is responsible for the decrease in cardiac output with age (Brandfonbrener, Landowne, & Shock, 1955; Granath, Jonsson, & Strandell, 1964; Strandell, 1964). Data are limited in the elderly on changes in resting stroke volume or cardiac output. Hagberg et al. (1989) found that elderly hypertensives did not increase their resting stroke volume or their plasma volumes after 9 months of low- or moderate-intensity exercise training. Their low-intensity exercise group had a reduction in resting cardiac output, while the moderate-intensity group had a reduction in total peripheral resistance. Schocken, Blumenthal, Port, Hindle, and Coleman (1983) reported that neither cardiac output nor stroke volume at rest changed after training in the elderly. However, Carroll (1992) showed an increase in stroke volume in an endurance training group but a decrease in stroke volume with a combined endurance and strength training group. This resulted in an increase in cardiac output for the endurance training group and a decrease in cardiac output for the combined group.

More longitudinal research is needed in this area to determine the relation between chronic physical activity and the changes in resting stroke volume and cardiac output in the elderly. If endurance training does increase cardiac output, this in turn may also cause increased HBF in the elderly adult.

Peripheral resistance. Peripheral resistance is another factor that may cause changes in HBF. If vascular resistance decreases in the elderly adult with exercise training, perhaps more blood would be able to flow to the liver with a reduction in cardiac output. With aging there is an increase in arterial rigidity or stiffness due to a loss of elastin and an increase in collagen (Roach & Burton, 1959). This causes an increase resistance to cardiac output. However, regular exercise has shown to reduce resting systemic pressure in elderly adults by about 5 mmHg (Smith, 1981; Hagberg et al., 1989).

Mechanisms associated with these changes include a decrease in sympathetic nervous system activity, resetting and/or increased sensitivity of baroreceptors, altered distribution of blood volume, altered pressure-natriuresis, alterations in the renin-angiotensin axis, altered sensitivity of vascular alpha and beta receptors, and alterations in the release or actions of endothelium-derived vasorelaxants and vasoconstrictors (Kenney & Zambrsski, 1984; Bjorntorp, 1987; Tipton, 1991).

Altered distribution of blood volume. Another possible mechanism that may cause an increase in blood flow to the liver is a redistribution of the blood volume. It has been shown that trained muscles may become more efficient in extracting oxygen from the blood (Ekblom et al., 1968; Saltin et al., 1968). Clausen et al. (1973) have shown there is a decrease in exercise-induced vasodilation in exercising muscles of trained individuals which allows relatively more blood to the nonexercising muscles and splanchnic-renal areas during exercise than in untrained individuals.

Plasma proteins. Studies on the affect of exercise on the plasma protein AAG are lacking. If aging and disease increase the level of AAG, perhaps an exercise program would attenuate or cause a reduction of this protein, thereby allowing more free drug to bind to receptor sites in the body. This would result, conceivably, in a greater pharmacodynamic effect of the drug.

Studies on the affect of exercise on albumin have found this protein to increase with exercise. Convertino et al. (1980) found a 28 g training induced increase in protein content in their subjects after endurance training. Carroll (1992) also found a 20.6 g increase in her elderly subjects. Plasma protein increase of albumin is important in facilitating hypervolemia with training by providing an increased water binding capacity. However, the increases in albumin would decrease the bioavailability of propranolol. Whether the increases in albumin with changes in AAG, with exercise, would change the bioavailability of propranolol is unknown.

Metabolizing enzymes. Castleden et al. (1975) suggested that elderly subjects had a greater concentration of propranolol due to a substantially reduced first-pass effect. Data are limited on whether the effect of regular exercise on drug metabolism at rest can be changed. Boel et al. (1984) believe that improved physical fitness can increase the hepatic elimination of low clearance drugs such as antipyrine and possible aminopyrine. Whether elimination of high clearanced drugs can be changed with exercise in humans is unknown.

In rats undergoing endurance training, i.e., swimming or running, regular activity increased the concentration or activity of some of the components of the hepatic microsomal monooxygenase system (Frenkle, Gyore, & Szeberenyi, 1980). One group of rats had to swim for 1 hour a day with 4 g/100 g body weight of additional weight and the second group of rats ran daily on a treadmill for 30 min set at a speed of 50 m/min and a grade of 14%. After 6 weeks of either swimming or running both groups of rats increased the cytochrome P_{450} concentration in the liver. Frenkle et al. (1980) concluded that exercise training caused enzyme induction in the liver of the rats. Another study by Ardies, Morris, Erikson, & Farrar (1989) found that after 7 weeks of running rats on a treadmill, 27m/min for 20 min initially progressing up to 60 min 5 times a week, increased the rates of ethanol clearance. They concluded that the chronic exercise increased *in vitro* ethanol metabolism by increasing the cytochrome P450 dependent monooxygenase system of hepatic microsomes.

It is not known if these results from an animal model can be extrapolated to humans. There is a need for longitudinal, carefully regulated experimental studies on the role of physical activity in delaying or decreasing the decrements in liver blood flow and metabolism in the elderly. Whether one can reverse the deleterious effects of aging or inactivity on HBF and drug metabolism is the primary concern of this study.

Summary

1. Hepatic blood flow decreases with age. Reduction in HBF may be due to decreases in plasma volume, stroke volume, cardiac output, and increases in vascular resistance.
2. Propranolol concentrations are higher in the elderly than the young after oral administration. Increases in concentration of propranolol are due to decreases in HBF, decreases in first pass effect, and decreases in the metabolizing enzymes of the liver.
3. Albumin and AAG are the plasma proteins that bind propranolol. With aging, data are conflicting about the changes of the plasma proteins and may depend on the health status of the elderly individual.
4. One cross-sectional study found no differences in HBF between trained and untrained individuals.
5. There are no human longitudinal studies that examine the effects of exercise training on HBF, propranolol concentrations, and the serum concentrations of the plasma protein AAG in young and elderly adults.

CHAPTER 3
METHODOLOGY

Subjects

Fifty five subjects (29 young [15 men and 14 women] and 26 elderly [13 men and 13 women]) were recruited from the Gainesville and Alachua County areas. Subjects were volunteers and were recruited by word of mouth, newspaper advertisement, and flyers. Subjects were between the ages of 19 to 40 and 60 to 80 years. Subjects were healthy with no contra-indications to exercise testing and training. Procedures for this study were approved by the University of Florida College of Medicine Institutional Review Board (Appendix A).

Subjects were screened by telephone before being accepted into the study. Criteria for the exclusion of subjects were as follows; 1) history or presence of cardiovascular, pulmonary, or peripheral vascular disease; 2) previous myocardial infarction, coronary artery bypass surgery, angina pectoris, or percutaneous transluminal coronary angioplasty (PTCA); 3) ST-segment depression or elevation at rest greater than 1mm or abnormal Q waves at rest; 4) more than 3 mm ST-segment depression from baseline during or after a maximal exercise test; 5) taking medication such as digitalis, beta blockers, or calcium blockers; 6) if subjects are on some type of medication they need to have been on it for a period of 3 months prior to the start of the study; 7) sinus bradycardia or heart block greater than first degree; 8) congestive heart failure; 9) ambulatory or orthopaedic limitations to exercise; 10) insulin-dependent diabetes; 11) blood pressure at rest greater than 160/100 mmHg; 12) history of allergy to indocyanine green, Evans blue, or propranolol; 13) history of Raynaud's syndrome; 14) history of malignant hypertension; 15) bronchial asthma; 16) active hepatic disease as indicated by any of the following a) AST (SGOT) or ALT (SGPT) greater than two times the upper limit of normal b) serum bilirubin greater than 1.5 times the upper limit of normal and c) serum albumin less than 3.0 mg/dl; 17) history of alcohol or drug abuse; 18) any condition which, in the opinion of the investigator makes participation in the study not in the patient's best interest; and 19) trained (conditioned, fit) subjects. If subjects met any of the above conditions they were not able to participate in the study.

Subjects who were suitable for the study reported to the Center for Exercise Science in the Florida Gymnasium at the University of Florida for orientation which lasted approximately 1 hour. At this time the entire study protocol, the inherent risks and hazards of the study, and the necessary time commitments were explained. Subjects were asked to complete demographic, medical history, family history, nutritional, smoking, and physical activity questionnaires (Appendix B). These forms were reviewed by the investigator. Subjects not meeting the requirements of the study were notified and were excluded. Documented informed consent was obtained from all subjects who wished to continue (Appendix C). Subjects were then scheduled for a further screening visit and were given instructions for subsequent visits to the laboratory (Appendix D). Subjects were asked to fast 12 hours before coming to the laboratory, to refrain from vigorous exercise 24 hours prior to testing, and to wear clothes that were comfortable for exercising.

For the screening visit the subjects reported to the laboratory in the morning for approximately 2 hours. During this visit and subsequent visits subjects completed 24 hour history questionnaires before testing (Appendix E). Previous completed questionnaires obtained during the orientation, were reviewed by a physician. The physician then administered a physical and cardiovascular examination, including a resting 12-lead electrocardiogram (ECG). After the examination, 15 ml of blood were drawn for a blood chemistry screening. The test included a complete blood count, serum electrolytes, BUN, creatinine, and liver function tests (AST, ALT, bilirubin, alkaline, phosphatase,total cholesterol, trigylcerides, albumin).

If any clinically significant findings such as abnormal blood tests, hypertension (blood pressure [BP] exceeding 160/100 mmHg at rest), angina pectoris, or an abnormal resting ECG (ST segment depression or elevation, *i.e.* horizontal or downsloping greater than 1mm, 0.08 seconds from the J-point, or the presence of abnormal Q waves) were found, the subjects were not allowed to continue in the study. Based on abnormal blood liver function tests (n=2; one young and one elderly) and resting ECG (n=1; elderly) three subjects were disqualified from the study.

Following the above baseline evaluations subjects underwent a graded exercise test (GXT) using a modified Naughton (2 min stages) (Naughton & Haider, 1973) or Bruce (Bruce, Kusumi, & Hosmer, 1973) protocol. The modified Naughton protocol is a walking protocol and was used on the subjects that were 60 to 80 years of age. The Bruce protocol is a walking and running protocol which was used on the subjects that were 19 to 40 years of age. Heart rate (HR) and ECG were monitored continuously throughout exercise and recovery periods using a 12-lead ECG system (Quinton 4000 Instruments, Seattle WA). Heart rate rhythm strips were taken during supine rest (standard and exercise set), sitting, after 20 sec of hyperventilation, and while standing. A 12-lead rhythm strip was recorded over the last 10 sec at each stage of exertion, at peak exercise, and at each minute for 7 minutes of recovery; a 3-lead rhythm strip was recorded at the intermediate minute of each exercise stage. Blood pressure was measured by auscultation during the supine, sitting, and standing positions. Blood pressures were also taken before every stage change during exercise, immediately post-exercise, and at minutes 1, 3, 5, and 7 of recovery. Ratings of perceived exertion (RPE) using the Borg scale (Borg, 1982) were obtained from the subjects every minute during exercise. The GXT was terminated when the individual reached maximal exertion or if signs and symptoms warranted the test to be stopped (ACSM, 1991).

Indications for stopping the GXT were development of 1) angina pectoris; 2) ataxia; 3) pallor; 4) symptomatic supraventricular tachycardia; 5) horizontal or down sloping ST segment depression that is greater than 3 mm at 0.08 seconds after the J point; 6) second or third degree heart block; 7) new onset of bundle branch block; 8) ventricular couplets (more than 2 per min); 9) ventricular tachycardia; 10) R on T phenomenon; 11) more than 10 unifocal preventricular contractions (PVCs) per min; 12) more than four PVCs per min; 13) blood pressure in excess of 250/110 mmHg; and 14) a drop in systolic blood pressure with an increasing workload (ACSM, 1991). In case of an emergency the laboratory was equipped with a crash cart containing all the appropriate medications and defibrillator immediately adjacent to the treadmill.

Based on the results of the GXT (significant ST segment depression during exercise) two elderly subjects were not allowed to continue and were referred to a physician for further testing and treatment. One young subject after successfully completing the screening decided not to continue with the study and one elderly subject was killed in a car accident. Thus, of the 55 subjects screened 48 (27 young [14 men and 13 women] and 21 elderly [10 men and 11 women]) were accepted into the study.

Methods of Data Collection

Blood Pressure Measurements

Resting BP measurements were taken in the morning before breakfast and coffee. Subjects were seated with their arms supported on a table in a small quiet room for 15 min. A Hawksley random zero sphygmomanometer (Hawksley, England) was used to determine resting BP on the subject's left arm. Two BP measurements were taken with at least a one min rest period between each measurement. If the two BP measurements were more than 6 (systolic BP) or 4 (diastolic BP) mmHg greater than each other a third BP measurement was taken. The two closest measurements were then averaged for the resting BP. A seated resting HR was also taken during this time. After the seated measurements were taken the subjects stood for a one min period and both a standing HR and BP were taken. Subject's resting BP measurements were taken on two separate visits. If the BP measurements from the two visits were greater than 8 mmHg for systolic and 6 mmHg for diastolic the subjects had to return to the laboratory for an additional visit to measure resting BP. The two closest measurements from the three days of testing were averaged for the required resting BP.

Body Composition

Body composition measurements were taken following the resting BP measurements. Measurements of skinfold fat thickness were made with

Lange calipers (Cambridge, MA) at the chest, axilla, triceps, subscapular, abdominal, suprailliac, thigh, suprapatella, and calf, following the procedures outlined by Pollock and Wilmore (1990). Measurements from the first 7 sites were summed ($\Sigma 7$). Body circumferences were measured with a steel tape at the shoulder, waist, gluteus, right thigh, right arm, and wrist following the procedures outlined by Pollock and Wilmore (1990).

Plasma Volume Measurement

Plasma volume measurements were taken after the measurement of body composition. During this procedure subjects assumed a supine position on a stretcher. A 20 or 22 G type angiocatheter (IV catheter) attached to a saline lock for blood sampling was inserted into a small vein in one of the forearms of the subjects. After insertion of the angiocatheter the subject remained in the supine position for 30 min. After the 30 min period a butterfly infusion kit was used to intravenously inject a 2.5 ml bolus of Evans blue dye, in the opposite arm. The butterfly was removed and exactly 10 min after the dye injection, a 6 ml blood sample was collected from the saline lock. Blood was collected in a plastic syringe and transferred to a sodium heparinized vacutaner (Vacutaner, Becton-Dickinson, Rutherford, NJ). Two small blood samples were placed in heparinized microcapillary tubes and microcentrifuged (IEC, Model MB, needham Heights, MA) for 5 min. The hematocrit (HCT) was determined by using a Fisher Micro-capillary Tube Reader. The remaining blood was centrifuged (Jouan BR3.11, Winchester, VA) at a speed of 3000 r/min for 10 min. Separated plasma was pipetted and stored in 12x75 mm polypropylene tubes at -20°C to be analyzed at a later date for the determination of plasma volume. After the blood sample was taken the catheter was removed.

Plasma volume analyses using Evan's blue dye (T-1824) was based on the methods of Young, Juhos, Castle, Yusken, and Greenleaf (1973) and Greenleaf, Convertino, and Mangseth (1979). The dye from the plasma sample was extracted onto a wood-cellulose powder (Solka Floc SW 40A) chromatographic column after it had been separated from the albumin by the action of a detergent (Teepol 610 in 2% Na_2HPO_4). Interfering substances such as pigments, proteins, and chylomicrons were washed from the column with 2% Na_2HPO_4. The dye was then eluted from the column with 1:1 acetone-water mixture. The addition of KH_2PO_4 buffered the pH of the eluate to 7.0; absorbance of the eluate was read at 615 nm. Plasma volume was calculated from the following formula:

$$PV = \frac{(V \times D)(St \times v)}{1.03(T)}$$

where

V = volume (ml) of T-1824 dye injected (22.6 mg/5ml)
D = dilution of standard (1:250)
St = absorbance of standard
v = volume of sample extracted (1.0ml)
T = absorbance of plasma sample
1.03 = correction factor for dye uptake by tissues

Blood volume (BV) was calculated as (PV)(100)/[100 - (0.91xHct)]).

Red cell volume (RCV) was calculated as BV(Hct)/100.

Maximal Oxygen Uptake Test

On a separate day from the screening GXT, maximal oxygen uptake (VO_2max) was determined using the Bruce or modified Naughton protocol. For those older individuals who exercised longer than 12 min on the initial modified Naughton protocol during their screening, the initial speed was set at 3 mph rather than 2 mph. The VO_2max test was again terminated when the subjects were unable to continue or signs and symptoms warrant test termination (ACSM, 1991). During the test, expired air was routed through a Medical Graphics (model CPX, St. Paul, MN) metabolic cart for measurement of oxygen and carbon dioxide gas concentrations and ventilatory volumes. Expired air was also collected in meteorological balloons minute by minute during the last few minutes of exercise. The concentrations of oxygen and carbon dioxide in the meteorological balloons were determined using the Ametek-Thermox (Pittsburg, PA) gas analyzers. The metabolic cart and the component gas analyzers were calibrated with primary standard mixtures. Ventilatory volumes were measured using a 120 L Tissot spirometer (Collins, Braintree, MA). All subjects met at least two of the following criteria for the determination of VO_2max: 1) a maximal HR at or above age predicted (220-age); 2) a respiratory exchange ratio greater than or equal to 1.1; and 3) a leveling off of VO_2 during the last minute of the test (change in $VO_2 \leq$ 200ml). Heart rate, BP, ECG, and RPE were monitored during rest, exercise, and recovery as in the initial GXT.

Hepatic Blood Flow and Propranolol Measurement

Hepatic blood flow measurement. Subjects arrived at the laboratory following an overnight fast and assumed a supine position on a stretcher. One 20 G type angiocatheter (IV catheter) attached to a saline lock for blood sampling was inserted into a small vein in the subject's forearm. The subject remained in the supine position for 30 min. After 30 min, 12 ml of blood was drawn from the saline lock for plasma baseline references of $alpha_1$ acid glycoprotein, propranolol, and ICG dye. Three ml of plasma were needed for alpha_1 acid glycoprotein, 2 ml for propranolol, and 1 ml for ICG. After the baseline collection, a butterfly infusion kit was used to administer intravenously a bolus of ICG dye (0.5 mg/kg body weight), in the arm opposite the catheter. After the injection of ICG dye, 4ml of blood was collected from the saline lock with a plastic syringe and transferred to a sodium heparinized vacutaner at 3 min intervals for 30 min. The collected blood along with the blood taken for the baseline were centrifuged (Jouan BR3.11, Winchester, VA) at a speed of 3000 x g for 10 min. The separated plasma was pipetted and stored in 12 x 75 mm polypropylene tubes at -20°C to be analyzed at a later date for the determination of liver blood flow. Blood pressure and HR (using a standard lead system) were recorded before the baseline blood draw and at 3, 15, and 30 min following the injection of the ICG dye (Data collection form, Appendix F).

Hepatic blood flow analyses. 1.0 µg of diazepam (internal standard) was added to 100 µl of methanol. Proteins were precipitated with acetonitrile (1 ml plasma - 1 ml acetonitrile) and the sample was centrifuged. The supernatant of ICG was analyzed by absorption spectrophotometry at a wavelength of approximately 800 nm (Caesar et al., 1961, Behme, Kensler, Brooke, 1982). Samples were analyzed using a double beam spectrophotometer equipped with a red-sensitive photomultiplier.

Plasma clearance of ICG (CL_{ICG}) was calculated by multiplying the plasma volume determined by Evan's blue by K_e, the elimination rate constant.

$$K_e = (0.693/t_{1/2})$$

$$CL_{ICG} = K_e \times PV$$

HBF was estimated as

$$EHBF = \frac{CL_{ICG}}{0.74(1-HCT)}$$

where HCT is the hematocrit and 0.74 is the mean extraction ratio of ICG obtained by direct measurement in normal subjects (Caesar et al., 1961; Grainger et al., 1983; Wynne et al., 1990).

Propranolol measurement. Following the HBF measurement, the subjects were given one 80 mg dose of propranolol by mouth with water. The subjects were kept in a recumbent position during the first 2 hours after the administration of the propranolol. Five ml of blood were drawn at 30 min, 1 hr, 1 hr and 30 min, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, and 10 hr. From these blood samples, plasma was obtained to determine plasma concentrations of propranolol. Blood pressure and HR were also taken and recorded at the same time interval as the blood samples. At hour 2 an additional 6 mls of blood was drawn for use in analyzing the protein binding of propranolol. After the second hour of the propranolol measurement test, subjects were allowed to get up and were given a light breakfast. Twenty minutes before each blood sample the subjects returned to a supine position on the stretcher. All blood samples were collected in 6 or 12 cc plastic syringes and transfered to sodium heparinized vacutaners. The collected blood was centrifuged (Jouan BR3.11, Winchester, VA) at speed of 3000 x g for 10 min. The separated plasma was pipetted and stored in 12 x 75 mm polypropylene tubes at -20°C to be analyzed at a later date for the determination of propranolol concentrations.

Propranolol measurement. Each sample was analyzed by liquid chromatography using a Nucleosil C_{18} column and UV-detection at 238 nm and at 295 nm. The mobile phase consisted of acetonitrile-methanol-ammonium chloride (0.04 M)-triethylamine (24:40:36:0.08, v/v/v/v). After the four mobile-phase components were mixed, phosphoric acid (85%, g/g) was used to adjust the pH to 6.9. The flow rate was 1.0 ml·min^{-1} and imipramine was used as the internal standard (Ververs, Schaefer, Lefevre, Lopez, & Derendorf, 1990). 1 ml of plasma was alkalinized with 0.6 ml borate buffer (0.1 M, pH 8.9) and 0.5 g sodium chloride, 50 µl imipramine HCL (10 µg·ml^{-1}) and 6 ml hexane-n-butanol (96:4, v/v) was added. The tubes were shaken for 10 min and were centrifuged for 10 min at 1500 g. The organic phase was removed and back extracted with 180 µl sulphuric acid (5 mM). After shaking (10 min) and centrifugation (10 min, 1500 g) 20 µl of the acidic aqueous phase was analyzed by liquid chromatography (Ververs et al.,1990).

Calibration curves were derived from pooled human plasma by adding appropriate amounts of propranolol in acetonitile-water (33:67, v/v) and 50 µl of internal standard solution (10 µg·ml^{-1}). Calibration curves were obtained by plotting peak-height ratios of drug to the internal standard versus concentration of the drug. The intra- and interday variability was evaluated by repetitive analysis of spiked human plasma samples at different drug concentrations. For the interday variability the spiked plasma samples were analyzed every other day over 2 weeks (Ververs et al., 1990).

Protein binding measurement. The HLPC system and instruments used for extraction followed procedures outlined for propranolol measurements. Centricon-30 concentrators (30,000 MW cut-off) (Amicron, Inc.) and a centrifuge with fixed-angle rotor (Beckman model J-6 with a JA rotor) were used to obtain the free propranolol. A plasma pool was prepared mixing the samples obtained at 1.5, 2, and 3 hours after dosing.

Randomization of Subjects

Three subjects of the 48 subjects that were allowed to participate in the study could not complete initial testing thus were dropped from the study. The 45 subjects (24 young [12 men and 12 women] and 21 elderly [10 men and 11 women]) who completed the initial testing were randomly assigned to either a control or training group. The training groups consisted of n=12 young and n=11 elderly subjects. The control groups consisted of n=12 young and n=10 elderly subjects. The control groups were offered the option to join an exercise program at the completion of the study. All groups were asked not to change their lifestyles (e.g., diet and exercise habits) during the 4 months of training or control periods.

Training

Training sessions were held three times a week for 16 weeks. The exercise groups performed dynamic exercise by walking on a treadmill (Trackmaster™) and/or stairclimbing (Stairmaster ™). All exercise sessions were held at the Living Well Center in the Florida Gymnasium at the University of Florida and were supervised by designated staff. During the initial weeks of training all subjects were taught appropriate warm-up and cool-down techniques and how to monitor their HRs by palpating their pulses. All subjects began their workouts with 5-10 minutes of stretching and calisthenics. An accurate log of all training activities including resting and training HRs, RPEs, intensities and durations of workouts were recorded. Exercise HRs and RPEs were monitored midway into and at the end of each training session.

Exercise intensity was established by the Karvonen formula (Karvonen, Kentala, & Musta, 1957) or percent of maximum heart rate reserve (%HRRmax) method. Subjects started aerobic training at 50% of their HRRmax. As they continued through the training program workout intensity was slowly increased until 80-85% of HRRmax was achieved. Workout intensity was increased by increasing the speed and/or grade on the treadmill and by increasing the level on the stairmaster. Increases in duration were made approximately every 2 weeks until week 8-9 when all subjects were exercising for a total of 40 min.

Training Schedule:

Week	%HRR	Duration (min)
1-2	50-60%	20
3-4	60-70%	25
5-6	60-70%	30
7-8	60-75%	35
9-10	70-80%	40
11-12	70-80%	40
13-14	75-85%	40
15-16	75-85%	40

Statistical Analyses

The Statistical Analyses System (SAS, 1985) was used for the management and analyses of data. Statistical significance was accepted at $p \leq 0.05$. Descriptive data were analyzed using One-Way Analyses of Variance (ANOVA) to compare elderly and young subjects and to compare the exercise and control groups in the elderly and young. To analyze the measured parameters of estimated HBF (ml/min), plasma concentrations of propranolol (ng/ml), peak plasma concentrations (ng/ml), albumin (mg/dl), plasma volume (ml/kg), HCT (%), blood volume (ml/kg), red cell volume (ml), VO_2max (L/min & $ml \cdot kg^{-1} \cdot min^{-1}$), body composition of sum of 7 skinfolds (mm), resting HR (b/min), resting BP (mmHg), and HRmax (b/min), a 2x2 Factorial Analysis of Covariance (ANCOVA) was used. ANCOVA was used due to the differences in values between the exercise and control groups on the initially measured parameters. The covariate, therefore, being the initial (T1) values. Interactions of main effects of treatment and age were further analyzed by an One-way ANCOVA separated by age. Within group comparisons were analyzed using a repeated measures ANOVA. A 4x2 repeated measures ANOVA was used to analyze if there were changes in BP and HR due to the single dose of oral propranolol. Interaction and main effects of BP and HR were analyzed using the Contrast multiple comparison test at $p \leq 0.01$.

CHAPTER 4
RESULTS

Subject Characteristics

Two of the 45 subjects did not complete the entire 4 months of training and therefore were eliminated from the final analyses. Descriptive data for the remaining 43 subjects are presented in Table 4.1. The young subjects were 7.0 cm taller than the elderly subjects. Weight and the sum of seven (Σ7) skinfolds were not different between the young and elderly. When the young and elderly subjects were randomly assigned to their control and training groups, the Σ7 skinfolds were not different between groups whereas, the young controls were taller and heavier than the young trainers. Characteristics of the two elderly groups were not different.

Table 4-1. Characteristics of the Young and Elderly Subjects

Group	Age (yrs)	Height (cm)	Weight (kg)	Skinfold Fat (mm)
Young				
Control (n=11)	31.5±5.1	177.3±9.6§	82.5±24.0§	175.9±62.7
Exercise (n=12)	29.1±5.1	168.8±6.1	66.4±8.9	155.6±51.7
Combined	30.2±5.2*	172.8±8.9*	74.1±19.2	165.3±56.7
Elderly				
Control (n=10)	67.8±5.1	165.2±12.8	78.3±14.6	196.7±70.2
Exercise (n=10)	66.3±5.6	166.4±11.3	70.4±13.1	187.9±52.8
Combined	67.1±5.3	165.8±11.7	74.4±14.1	192.3±60.6

Values are mean ± S.D.

Skinfold Fat = Σ7 sum of seven skinfolds (triceps, chest, subscapula, axilla, abdomen, suprailium, thigh).

*p≤0.05, different from elderly.

§p≤0.05, young controls different from young trainers.

Training Responses

Training Stimulus

Training intensity and perception of effort averaged over 4 week intervals are presented for the young and elderly in Table 4-2. During the 5th to 8th week of training the young subjects were training at a greater intensity than the elderly group (p=0.03). During the other time periods the training stimuli were not different between the two training groups. The RPEs for the training stimuli were also not different between the two training groups.

Table 4-2. Training Intensity and Perception of Effort for the Young and Elderly Subjects (n=22).

Variables	Young (n=12)	Elderly (n=10)
%HRR		
Week 1-4	64.4 ± 3.5	62.2 ± 5.1
Week 5-8	76.3 ± 2.0	72.9 ± 4.6*
Week 9-12	80.2 ± 4.2	77.3 ± 4.8
Week 13-16	82.8 ± 3.1	79.9 ± 4.1
RPE		
Week 1-4	12.7 ± 0.9	13.2 ± 1.2
Week 5-8	13.6 ± 1.3	14.8 ± 2.0
Week 9-12	14.4 ± 15.5	15.5 ± 2.4
Week 13-16	14.6 ± 1.7	16.1 ± 2.5

Values are mean ± S.D.
*$p \leq 0.05$, less than young.
%HRR=percent of maximal HR reserve.
Values for RPE are Borg (1982) scale units.

Parameters from the Maximal Oxygen Uptake Test

Initial values obtained from the VO_2max test for the young and the elderly are presented in Table 4-3. Maximal data for HR, VO_2, VE, oxygen pulse, and RER were higher, and systolic BP was less in the young than the elderly subjects ($p \leq 0.05$). There were no differences in the maximal diastolic BP and RPE.

Table 4-3. Physiological Parameters Obtained During the Initial Maximal Exercise Test in the Young and Elderly Subjects (N=43).

Variable	Young (n=23)	Elderly (n=20)
HRmax	190 ± 8*	155 ± 17
VO2max Absolute	2.68 ± 0.88*	1.73 ± 0.51
VO2max Relative	35.8 ± 5.9*	23.3 ± 5.8
VEmax	96.5 ± 28.0*	65.2 ± 23.9
Max. Oxygen Pulse	14.1 ± 4.6*	11.3 ± 3.4
RERmax	1.22 ± 0.06*	1.15 ± 0.10
SBPmax	166 ± 22*	187 ± 20
DBPmax	79 ± 13	77 ± 10
RPEmax	19.5 ± 0.7	19.5 ± 0.7

Values are mean ± S.D.
HRmax=Maximal Heart Rate (b/min); VO2max Absolute=Absolute Maximal Oxygen Uptake (L/min); VO2max Relative=Relative Maximal Oxygen Uptake (ml·kg^{-1}·min^{-1}); VEmax=Maximal Ventilation (L/min); Max. Oxygen Pulse (ml/beat); RERmax=Maximal Respiratory Exchange Ratio; SBPmax=Maximal Systolic Blood Pressure (mmHg); DBPmax=Maximal Diastolic Blood Pressure (mmHg); RPEmax=Maximal Rating of Perceived Exertion
*$p \leq 0.05$ different from elderly

Table 4-4 presents the maximal treadmill data before (T1) and after (T2) training separated by age and treatment. There were no age x treatment interactions for any of the measured parameters ($p > 0.05$). Data show that training improved VO2max relative and absolute in both young and elderly subjects relative to the controls. The increases in VO2max with training was associated with increases in maximal VE and maximal oxygen pulse in both the young and elderly training groups compared to the controls. The young training group also showed a decrease in maximal diastolic BP. Figure 4-1 illustrates the percent change in relative VO2max between age and treatment groups. The magnitude of the training response was not different between the young (12.5±3.6%) and elderly (13.6±5.5%) subjects.

Table 4-4. Maximal Treadmill Data Before (T1) and After (T2) Training for Young and Elderly Subjects (N=43).

Variables	Control T1	Control T2	Control Adjusted T2	Training T1	Training T2	Training Adjusted T2
Young (n=23)		(n=11)			(n=12)	
HRmax	192 ± 8	188 ± 6	187	188 ± 8	187 ± 8	188
VO_2max Abs.	3.093±1.110	3.185± 1.167	2.749	2.296±0.332	2.614± 0.384*	3.015§
VO_2max Rel.	37.1 ± 6.6	37.9 ± 6.4	36.6	34.7 ± 5.2	39.0 ± 6.0*	40.2§
VEmax	107.7± 33.7	117.8± 44.1	107.3	86.2 ± 17.1	99.5 ± 15.3*	109.1§
Max. O_2 Pulse	16.1 ± 5.8	16.8 ± 6.0	14.8	12.3 ± 2.3	14.0 ± 2.3*	15.9§
RERmax	1.22 ± 0.05	1.17 ± 0.07	1.18	1.22 ± 0.07	1.21 ± 0.09	1.21
SBPmax	174 ± 27	181 ± 29	175	158 ± 11	167 ± 14	173
DBPmax	81 ± 17	79 ± 14	80	77 ± 9	70 ± 7*	72§
RPEmax	19.4 ± 0.9	19.5 ± 0.5	19.4	19.6 ± 0.5	19.8 ± 0.4	19.6
Elderly (n=20)		(n=10)			(n=10)	
HRmax	150 ± 19	149 ± 21	151	160 ± 15	160 ± 17	155
VO_2max Abs.	1.846±0.515	1.737± 0.447*	1.622	1.612±0.495	1.827± 0.571*	1.942§
VO_2max Rel.	24.0 ± 7.5	22.4 ± 6.6*	21.7	22.5 ± 3.7	25.6 ± 4.7*	26.3§
VEmax	67.5 ± 27.9	62.9 ± 25.6*	60.8	62.9 ± 20.4	64.6 ± 20.6	66.8§
Max. O_2 Pulse	12.4 ± 3.2	12.0 ± 2.8	10.9	10.2 ± 3.3	11.6 ± 4.1*	12.8§
RERmax	1.11 ± 0.09	1.02 ± 0.13	1.05	1.18 ± 0.10	1.00 ± 0.13	0.97
SBPmax	190 ± 18	195 ± 14	193	185 ± 22	193 ± 27	195
DBPmax	78 ± 8	80 ± 7	82	76 ± 12	73 ± 11	76
RPEmax	19.7 ± 0.5	19.4 ± 0.5	19.7	19.2 ± 0.8	19.5 ± 0.5	19.2

Values are mean ± S.D. HRmax=Maximal Heart Rate (b/min); VO_2max Abs.=Absolute Maximal Oxygen Uptake (L/min); VO_2max Rel.=Relative Maximal Oxygen Uptake ($ml \cdot kg^{-1} \cdot min^{-1}$); VEmax=Maximal Ventilation (L/min); Max. O_2 Pulse=Maximal Oxygen Pulse (ml/beat); RERmax=Maximal Respiratory Exchange Ratio; SBPmax=Maximal Systolic Blood Pressure (mmHg); DBPmax=Maximal Diastolic Blood Pressure (mmHg); RPEmax=Maximal Rating of Perceived Exertion; *$p \leq 0.05$ different from initial (T1) values. §$p \leq 0.05$ different from control group.

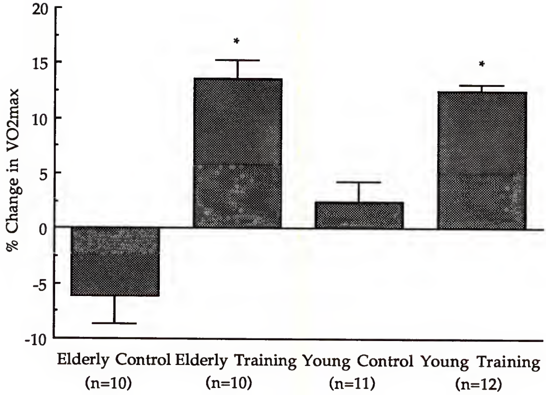

Figure 4-1. Percent changes in relative VO_2max for the control and training young and elderly subjects. Values are means ± S.E. *$p \leq 0.05$ different from control group.

Resting Data

Table 4-5 presents the cardiovascular resting data separated by age and treatment. There were no age x treatment interactions or age main effects for the measured parameters ($p > 0.05$). When comparing the training groups relative to the controls the young group decreased sitting diastolic BP and the elderly group decreased sitting HR and standing diastolic BP, after the 16 weeks of training.

Table 4-6 presents the resting plasma volume and blood volume data separated by age and treatment. Two subjects were not included in this

Table 4-5. Resting BP and HR Data Before (T1) and After (T2) Training for Young and Elderly Subjects (N=43).

Variables		Control			Training		
		T1	T2	Adjusted T2	T1	T2	Adjusted T2
Young (n=23)			(n=11)			(n=12)	
Sitting	SBP	112 ± 13	114 ± 14	106	99 ± 7	98 ± 7	104
	DBP	74 ± 12	76 ± 12	74	67 ± 8	66 ± 3	68§
	HR	70 ± 10	71 ± 6	70	66 ± 6	64 ± 11	65
Standing	SBP	115 ± 19	119 ± 17	110	105 ± 6	106 ± 10	113
	DBP	84 ± 15	84 ± 14	80	76 ± 5	73 ± 5†	76
	HR	78 ± 12	79 ± 8	79	78 ± 9	75 ± 11	75
Supine	SBP	119 ± 15	118 ± 14	115	110 ± 8	109 ± 10	113
	DBP	75 ± 13	76 ± 17	72	68 ± 7	68 ± 12	72
	HR	63 ± 7	63 ± 8	62	59 ± 9	57 ± 8	58
Elderly (n=20)			(n=10)			(n=10)	
Sitting	SBP	126 ± 21	127 ± 17	125	121 ± 15	119 ± 19	121
	DBP	74 ± 7	74 ± 8	73	71 ± 4	69 ± 4†	70
	HR	66 ± 8	68 ± 10	68	66 ± 10	62 ± 9*	62§
Standing	SBP	127 ± 21	134 ± 19	132	122 ± 13	121 ± 19	123
	DBP	81 ± 7	83 ± 9	82	79 ± 6	75 ± 6	75§
	HR	72 ± 12	74 ± 12	74	72 ± 12	70 ± 11	69
Supine	SBP	133 ± 20	133 ± 19	131	124 ± 18	124 ± 18	129
	DBP	78 ± 10	75 ± 7	73	70 ± 6	71 ± 6	73
	HR	61 ± 8	64 ± 10	63	60 ± 4	59 ± 6	59

Values are mean ± S.D. SBP=Systolic Blood Pressure (mmHg); DBP=Diastolic Blood Pressure (mmHg); HR=Heart Rate (b/min). *$p \leq 0.05$ different from initial (T1) values. §$p \leq 0.05$ different from control group. †$p = 0.06$ different from initial (T1) values.

Table 4-6. Evan's Blue Measurements of Resting Plasma and Blood Volume Data Before (T1) and After (T2) Training for Young and Elderly Subjects (N=41).

Variables	Control T1	T2	Adjusted T2	Training T1	T2	Adjusted T2
Young (n=23)		(n=11)			(n=12)	
Hct	42 ± 3	42 ± 3	41.4	40 ± 2	38 ± 2*	39§
PV	3255 ± 804	3247 ± 796	2943	2670 ± 274	3079 ± 374*	3359§
PV/kg	40 ± 6	40 ± 5	40	40 ± 6	46 ± 8*	46§
BV	5319 ± 1417	5315 ± 1396	4732	4199 ± 448	4729 ± 570*	5264§
BV/kg	65 ± 10	65 ± 7	64	63 ± 10	71 ± 12*	72§
RCV	2269 ± 686	2272 ± 682	1968	1680 ± 211	1813 ± 241*	2091§
Elderly (n=18)		(n=9)			(n=9)	
Hct	41 ± 2	40 ± 3	40	39 ± 2	38 ± 2*	38§
PV	3077 ± 845	3115 ± 750	2932	2679 ± 471	3014 ± 533*	3197§
PV/kg	39 ± 6	39 ± 5	39	39 ± 5	44 ± 7*	44§
BV	4921 ± 1322	4935 ± 1261	4574	4187 ± 806	4599 ± 911*	4960§
BV/kg	63 ± 10	63 ± 10	61	60 ± 8	67 ± 10*	68§
RCV	2026 ± 536	2000 ± 579	1803	1657 ± 377	1741 ± 423*	1938§

Values are mean ± S.D.

Hct=Hematocrit; PV=Plasma Volume (ml); PV/kg=Plasma Volume/kg of Body Weight (ml/kg); BV=Blood Volume (ml); BV/kg=Blood Volume/kg of Body Weight (ml/kg); RCV=Red Cell Volume (ml).

*$p \leq 0.05$ different from initial (T1) values.

§$p \leq 0.05$ different from control group.

analysis due to problems with the injection and sampling of dye. There were no age x treatment interactions or age main effects for the measured parameters (p>0.05). There were no differences in the initial blood parameters between the young and the elderly groups. After the 4 months of aerobic training both the young and elderly groups increased plasma volume, blood volume, RCV, and decreased HCT.

Figure 4-2 illustrates the percent change of blood volume with the control and training groups in the young and elderly. The elderly training group increased blood volume by 9.8±1.9% and the young increased by 12.5±1.4% (Values are mean ± S.E.). There was no difference in the percentage of change between the training groups and the control groups.

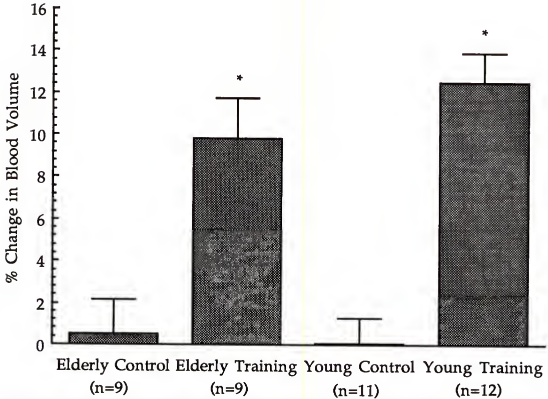

Figure 4-2. Percent changes in blood volume for the control and training groups of young and elderly subjects. Values are means ± S.E. $p \leq 0.05$ different form control group.

Estimated Hepatic Blood Flow

Initial values for the young and elderly estimated HBF parameters are presented in Table 4-7. Two elderly subjects were excluded from the analyses due to problems in acquiring plasma volume measurements. Another elderly subject was excluded due to problems in determining ICG concentrations in the plasma. The elimination rate constant (K_e) was significantly higher and the half-life of ICG was significantly shorter ($p \leq 0.05$) in the young when compared to the elderly. Clearance and estimated HBF were not significantly different between the young and elderly groups ($p > 0.05$).

Table 4-7. Physiological Parameters Obtained During Initial Baseline Measurement of Estimated HBF in the Young and Elderly Subjects (N=40)

Variable	Young (n=23)	Elderly (n=17)
K_e (1/hour)	0.19 ± 0.04	0.17 ± 0.03*
Half-life (min)	3.7 ± 0.7	4.2 ± 0.7*
Clearance (l/min)	0.57 ± 0.16	0.47 ± 0.15†
EHBF (ml/min)	1306 ± 378	1073 ± 354§

Values are mean ± S.D.
K_e=elimination rate constant.
EHBF=estimated hepatic blood flow.
*$p \leq 0.05$, different from young.
†$p = 0.07$, different from young.
§$p = 0.06$, different from young.

Data are presented for the young and elderly by treatment groups in Table 4-8. A significant age x treatment interaction was observed for clearance and estimated HBF. Post-hoc analyses (Table 4-8) found that the young training group had significantly higher values than the control group for clearance and estimated HBF, while the elderly group showed no changes in clearance

Table 4-8. Esimated HBF Data Before (T1) and After (T2) Training for Young and Elderly Subjects (N=40).

Variables		Control			Training	
	T1	T2	Adjusted T2	T1	T2	Adjusted T2
Young (n=23)		(n=11)			(n=12)	
K_e (1/hour)	0.20 ± 0.04	0.17 ±0.03*	0.16	0.19 ± 0.03	0.18 ± 0.03	0.18§
Half-life (min)	3.5 ± 0.7	4.2 ± 0.7*	4.3	3.8 ± 0.6	3.9 ± 0.7	3.8§
Cl (l/min)	0.64 ± 0.18	0.54 ±0.15*	0.49	0.50 ± 0.09	0.55 ± 0.08*	0.60§
EHBF (ml/min)	1504± 432	1269± 358*	1126	1123± 201	1207± 188†	1338§
Elderly (n=17)		(n=8)			(n=9)	
K_e (1/hour)	0.17 ± 0.03	0.16 ± 0.03	0.16	0.17 ± 0.03	0.16 ± 0.03	0.16
Half-life (min)	4.2 ± 0.8	4.4 ± 0.9	4.4	4.2 ± 0.7	4.6 ± 0.9	4.6
Cl (l/min)	0.51 ± 0.21	0.52 ± 0.19	0.50	0.44 ± 0.07	0.46 ± 0.08	0.48
EHBF (ml/min)	1169± 487	1184± 444	1119	987 ± 160	999 ± 170	1057

Values are mean ± S.D.

K_e=elimination rate constant; Cl=Clearance; EHBF= Estimated HBF.

*$p \leq 0.05$ different from initial (T1) values.

§$p \leq 0.05$ different from control group.

†$p = 0.07$ different from initial (T1) values.

and estimated HBF when compared to the elderly controls. Further analyses showed that the young exercise group also had a higher K_e value and a lower half-life than the young control group. When a within comparison was performed on the data for the young control and training groups, the control group decreased in clearance and estimated HBF while the training group increased in clearance but did not change estimated HBF (p=0.07). Decreases were also found in the control group for K_e and increases for half-life of ICG. No changes in K_e or half-life were seen with the group that trained. Figure 4-3 illustrates the changes in estimated HBF among the treatment groups in the young and elderly subjects.

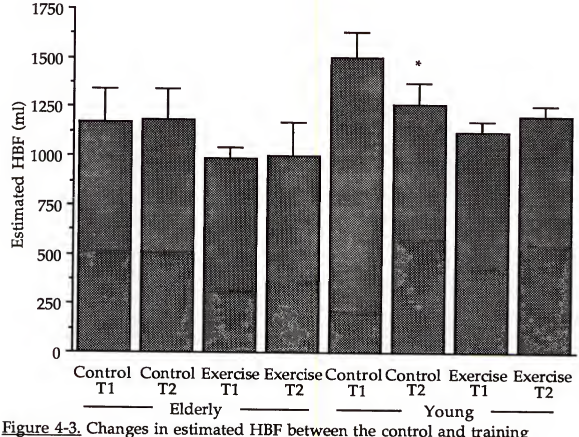

Figure 4-3. Changes in estimated HBF between the control and training groups of young and elderly subjects. Values are means ± S.E. *p≤0.05 different from initial (T1) values.

Propranolol Pharmacokinetics and Protein Binding After Oral Administration

Table 4-9 presents data on the elderly and young subjects after initial oral administration of 80 mg of propranolol. There were no significant differences between the young and the elderly in the pharmacokinetics of oral propranolol.

Table 4-9. Pharmacokinetic Parameters Obtained During Oral Administration of 80 mg of Propranolol Prior to Training (N=43).

Variable	Young (n=23)	Elderly (n=20)
AUC_∞	763 ± 287	1088 ± 639
C_{max}	102 ± 37	115 ± 62
T_{max}	2.24 ± 0.92	2.05 ± 0.69
AUC_{10}	558 ± 214	658 ± 369
Half-life	4.88 ± 1.48	5.87 ± 2.07†
$K_{4\text{-}10}$	0.15 ± 0.04	0.13 ± 0.05

Values are mean ± S.D.

AUC_∞=area under the curve extrapolated to infinity (ng/ml•hr); C_{max}=maximal concentration of propranolol (ng/ml); T_{max}=time at which maximal concentration occurs (hour); AUC_{10}=area under the curve to hour 10 (ng/ml•hr); Half-life=terminal phase half-life (hour) from hours 4 to 10; $K_{4\text{-}10}$=the elimination rate constant from hours 4 to 10.

†p=0.08, different from young.

There were no age x treatment interactions for the measured parameters of oral propranolol. The only main effect found was a treatment effect for the parameter of time to maximal concentration of propranolol in the elderly training group relative to the controls (Table 4-10). Figures 4-4 through 4-6 illustrate the concentration-time curves for oral propranolol.

Table 4-10. Pharmacokinetic Parameters Obtained During Oral Administration of 80 mg of Propranolol Data Before (T1) and After (T2) Training for Young and Elderly Subjects (N=43).

Variables	Control			Training		
	T1	T2	Adjusted T2	T1	T2	Adjusted T2
Young (n=23)	(n=11)			(n=12)		
AUC∞	799 ± 351	882 ± 452	844	729 ± 224	707 ± 307	742
Cmax	102 ± 41	112 ± 65	111	102 ± 36	94 ± 39	95
Tmax	2 ± 1.0	2 ± 0.9	2	2 ± 0.9	3 ± 1.0	3
AUC10	582 ± 238	608 ± 309	583	536 ± 198	515 ± 225	538
Half-life	5 ± 1.0	5 ± 1.8	6	5 ± 1.9	5 ± 2.9	5
K4-10	0.16 ± 0.04	0.14 ± 0.05	0.14	0.15 ± 0.04	0.16 ± 0.05	0.16
Elderly (n=20)	(n=10)			(n=10)		
AUC∞	868 ± 410	835 ± 379	939	1148± 806	964 ± 646	861
Cmax	105 ± 45	108 ± 46	112	126 ± 77	113 ± 57	109
Tmax	2 ± 0.7	2 ± 1.1	2	2 ± 0.7	3 ± 0.7*	3§
AUC10	580 ± 261	592 ± 257	645	735 ± 453	667 ± 391	615
Half-life	6 ± 1.6	5 ± 1.7	5	6 ± 2.5	5 ± 1.7	5
K4-10	0.13 ± 0.04	0.15 ± 0.06	0.15	0.14± 0.06	0.18 ± 0.10	0.17

Values are mean ± S.D.

AUC∞=area under the curve extrapolated to infinity (ng/ml•hr); Cmax=maximal concentration of propranolol (ng/ml); Tmax=time at which maximal concentration occurs (hour); AUC10=area under the curve to hour 10 (ng/ml•hr); Half-life=terminal phase half-life (hour) from hours 4 to 10; K4-10=the elimination rate constant from hours 4 to 10.

*$\underline{p} \leq 0.05$ different from initial (T1) values.

§$\underline{p} \leq 0.05$ different from control group.

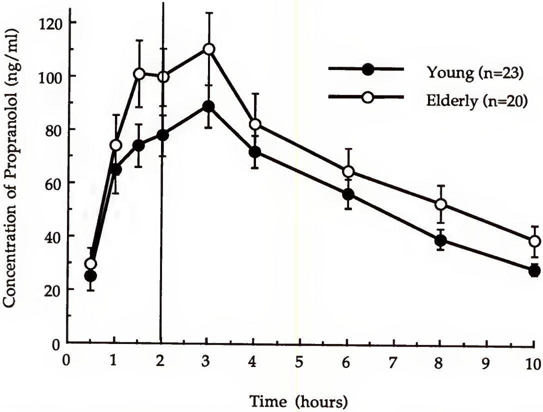

Figure 4-4. Concentration of propranolol at T1 across time for the young and elderly subjects. Values are mean ± S.E.

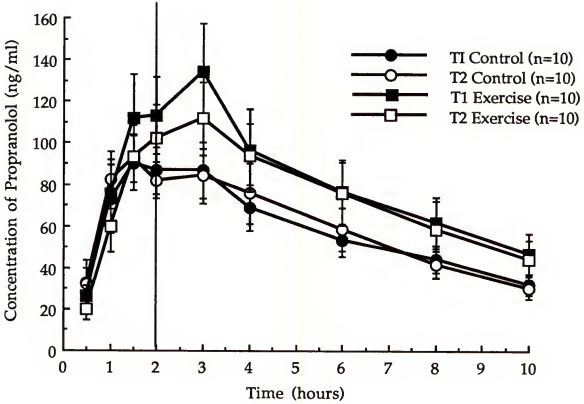

Figure 4-5. Concentration of propranolol across time for the elderly subjects in the control and training groups pre (T1) and post (T2) testing. Values are mean ± S.E.

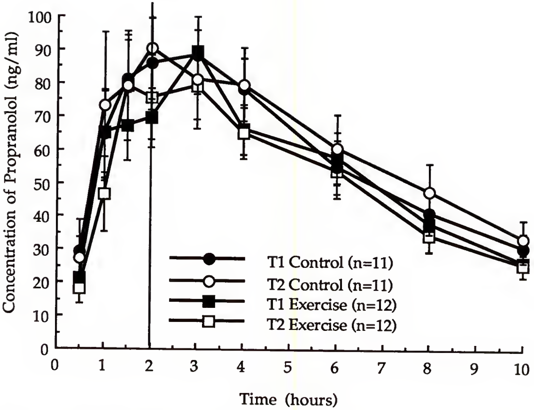

Figure 4-6. Concentration of propranolol across time for the young subjects in the control and training groups pre (T1) and post (T2) testing. Values are mean ± S.E.

Protein Binding

Table 4-11 presents the protein binding data for the elderly and young subjects. There were no differences in initial values of free and unbound drug between the young and elderly subjects. After the 16 weeks of exercise training there were also no differences in the groups that trained relative to the controls.

Table 4-11. Protein Binding Obtained During Oral Administration of 80 mg of Propranolol Data Before (T1) and After (T2) Training for Young and Elderly Subjects (N=43).

Variables		Control			Training	
	T1	T2	Adjusted T2	T1	T2	Adjusted T2
Young (n=22)		(n=11)			(n=11)	
% Free	5.7 ± 2.9	7.0 ± 2.5	7.9	8.2 ± 4.2	7.3 ± 3.9	6.4
% Bound	94.3 ± 2.9	93.0 ± 2.5	92.1	91.8 ± 4.2	92.7 ± 3.9	93.6
Elderly (n=20)		(n=10)			(n=10)	
% Free	7.9 ± 3.3	7.2 ± 2.4	6.8	6.3 ± 2.8	5.7 ± 1.8	6.1
% Bound	92.1± 3.3	92.8 ± 2.4	93.2	93.7± 2.8	94.3 ± 1.8	93.9

Values are mean ± S.D.

% Free=amount of drug not bound to protein.

% Bound=amount of drug bound to protein.

Physiological Responses to Oral Propranolol

Figures 4-7 through 4-15 present the HR, systolic, and diastolic BP data after oral administration of 80 mg of propranolol. During the first 2 hours after administration of propranolol HR and BP were taken every 30 min.. During those 2 hours subjects were fasting and resting in a supine position. After the second hour subjects were allowed to eat and move around. Since the next 8 hours were not well controlled, responses of HR and BP to propranolol were only analyzed on the first 2 hours; at 30 min, 60 min, 90 min, and 120 min.

There were no interactions, treatment, or time main effects for systolic BP. There was, however, an age main effect between the young and elderly in systolic BP. For diastolic BP there was an interaction effect between time and treatment. However, when contrasts were performed there were no significant differences among the time points. For HR there were time and treatment main effects. Contrasts found differences in HR for both the young and elderly groups (Figure 4-14 and 4-15).

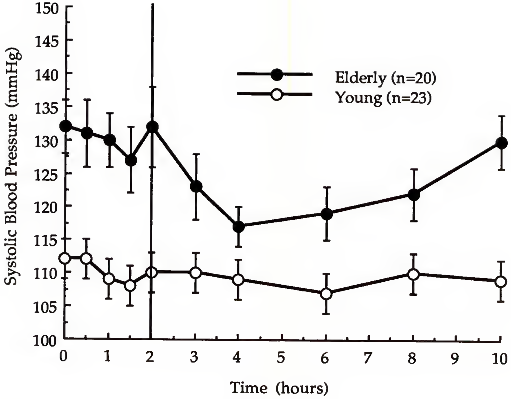

Figure 4-7. Mean responses of systolic BP in the young and elderly after administration of 80mg of oral propranolol. Values are mean ± S.E.

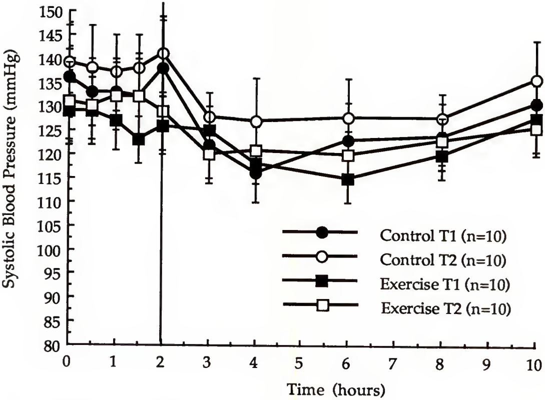

Figure 4-8. Mean responses of systolic BP for the elderly subjects in the control and training groups pre (T1) and post (T2) testing after administration of 80mg of oral propranolol. Values are mean ± S.E.

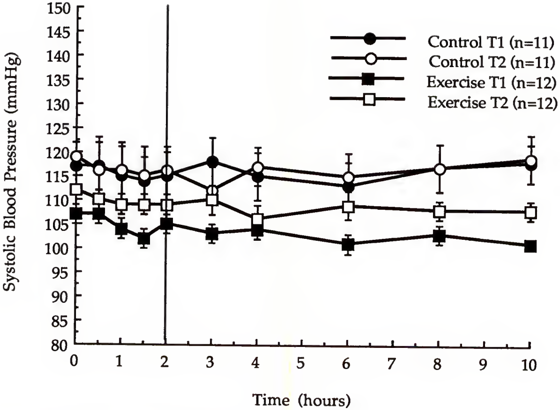

Figure 4-9. Mean responses of systolic BP for the young subjects in the control and training groups pre (T1) and post (T2) testing after administration of 80mg of oral propranolol. Values are mean ± S.E.

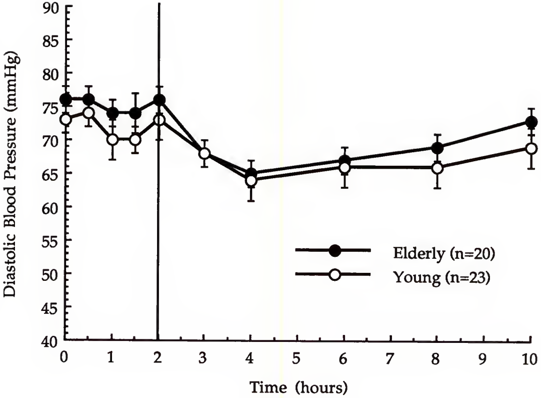

Figure 4-10. Mean responses of diastolic BP in the young and elderly after administration of 80mg of oral propranolol. Values are mean ± S.E.

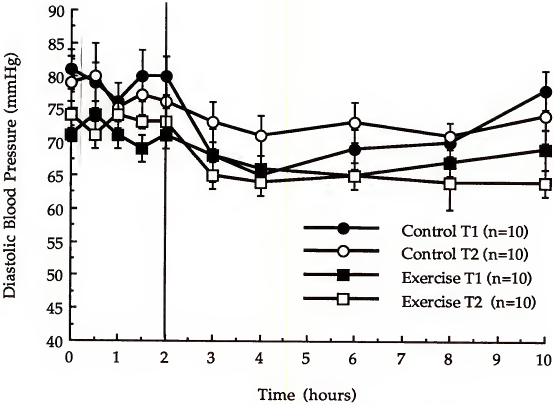

Figure 4-11. Mean responses of diastolic BP for the elderly subjects in the control and training groups pre (T1) and post (T2) testing after administration of 80mg of oral propranolol. Values are mean ± S.E.

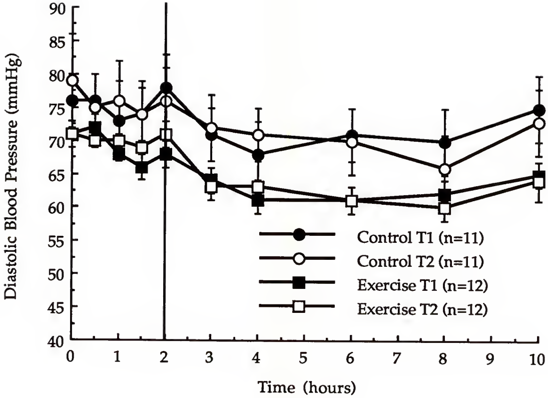

Figure 4-12. Mean responses of diastolic BP for the young subjects in the control and training groups pre (T1) and post (T2) testing after administration of 80mg of oral propranolol. Values are mean ± S.E.

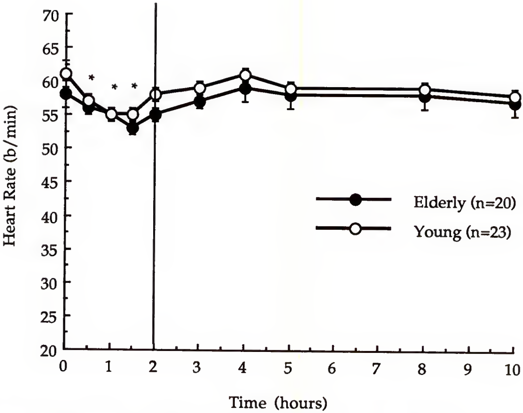

Figure 4-13. Mean responses of HR in the young and elderly after administration of 80mg of oral propranolol. Values are mean ± S.E. *$p \leq 0.05$ different from initial HR at time 0.

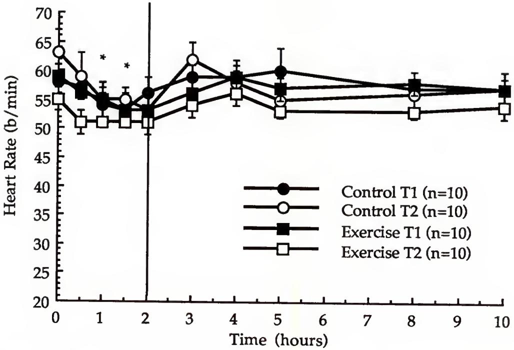

Figure 4-14. Mean responses of HR for the elderly subjects in the control and training groups pre (T1) and post (T2) testing after administration of 80mg of oral propranolol. Values are mean ± S.E. $*p \leq 0.05$ different from initial HR at time 0.

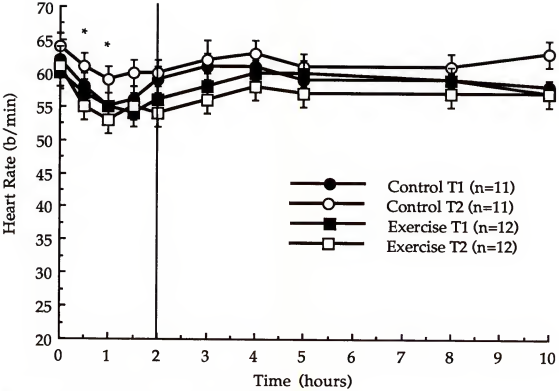

Figure 4-15. Mean responses of HR for the young subjects in the control and training groups pre (T1) and post (T2) testing after administration of 80mg of oral propranolol. Values are mean ± S.E. *$p \leq 0.05$ different from initial HR at time 0.

CHAPTER 5
DISCUSSION AND CONCLUSIONS

Training Responses

This study is the first longitudinal study to examine the effects of exercise training on estimated HBF and oral propranolol concentrations in young and elderly subjects. It is also one of the first studies to compare the effects of training on VO_2max, blood volume, plasma volume, and HCT using similar frequency, intensity, duration, mode, and length of training in young and elderly adults.

Maximal Oxygen Uptake

Both the young (12.5%) and elderly (13.6%) exercise groups showed similar improvements in VO_2max. These values are somewhat low compared to studies that have shown improvements ranging from 15-30% (ACSM, 1991). However, the length of time for training in this study was shorter, 4 months compared to 6 months or longer in similar studies (ACSM, 1991). Care was also taken to progress intensity and duration gradually to allow the elderly individuals time to adapt to the exercise and to prevent injuries.

Previous data from our laboratory have shown incidence of injuries ranging from 57% in 70-79 year olds in a walking/jogging program and 14% in 60-79 year olds in a walking program (Carroll, Pollock, Graves, Leggett, Spitler, & Lowenthal, 1992). In the present study no injuries due to training were reported. Therefore, the rate of progression, intensity, duration, and frequency of training was appropriate in keeping the subjects injury free. Although, the younger subjects could have tolerated more rapid progression and intensity, the design of this study was to provide similar training stimulus to the younger and older adults. The results of the study found that similar training stimulus produced similar relative improvements in VO_2max between the young and elderly training groups.

Resting Blood Pressure and Heart Rate

The data on resting BP in this study are consistent with other exercise training studies. Despite some reductions that are seen in a few normotensive individuals, it is commonly thought that the BP-lowering benefits that can occur with endurance training are dependent on the initial levels of BP. Therefore, those individuals with normal BP often do not achieve reductions (Grimby, & Astrand, 1969; Adams & deVries, 1973; Kilbom, Hartley, Saltin, Bjure, Pollock et al., 1976; Schocken et al., 1983) while those with mild to moderate elevations in BP (>140/90 mmHg) are likely to obtain improvements with training (Cononie, Graves, Pollock, Phillips, Sumners, & Hagberg, 1991).

A decline in resting HR after endurance training is well documented in young, middle-aged, and elderly subjects. The magnitude of the decrease ranges from 4 to 8 beats/min (Oscai et al., 1968; Hartley et al., 1969; Pollock et al., 1971; Adams & deVries, 1973; Pollock et al., 1976; Convertino et al., 1980a; Convertino et al., 1983; Hagberg et al., 1989; Seals & Chase 1989; Cononie et al., 1991; Convertino et al., 1991). In the present study, however, only the elderly decreased HR in the sitting position after the endurance program. Perhaps if more subjects were included in the study significance would have been achieved. All adjusted T2 values for supine, sitting, and standing HR were lower in the exercise groups, although not significant, compared to those adjusted values for the control groups.

Resting Plasma Volume, Blood Volume, and HCT

Few studies have documented the plasma volume responses to training in older individuals. Resting plasma volume does not appear to change with age up to age 40 (Chien et al., 1966) but cross-sectional and longitudinal data are lacking. Convertino et al., (1980a) hypothesized that training-induced hypervolemia might be less in older individuals due to a decrease in physical working capacity. Indirect evidence for this hypothesis was offered by data from Kilbom et al., (1969). In this study, 38-55 year old men, increased VO_2max by 14% after 2 months of endurance training with no changes in resting hemoglobin and HCT. Although plasma volume was not measured, the data suggest that it did not change since an increase in plasma volume is usually associated with decreases in hemoglobin and HCT (Oscai et al., 1968; Convertino et al., 1980a). A recent study by Carroll et al. (1992) was the first longitudinal study to look at the effects of exercise training on plasma volume in elderly men and women 60-80 years of age. They found similar values for plasma volume, blood volume, and HCT in the elderly as seen with younger adults. After 6 month of aerobic training their subjects increased VO_2max by 13-16% and increased plasma volume and blood volume by 9.5%.

The present study is the first study to look at the effects of similar training frequency, intensity, duration, mode, and length of program in young and elderly adults to responses in plasma volume, blood volume, and HCT. The training stimulus given to the young and elderly produced similar changes in plasma volume (E: 12.6±2.2%; Y: 15.2±1.6%) and blood volume (E: 9.8±1.9%; Y: 12.5±1.4%). The increases in plasma and blood volume are similar to the 9-12% increases that have been reported in previous studies for young and elderly adults (Convertino et al., 1980a; Convertino, 1980b; Convertino et al., 1991; Carroll et al., 1992). These data suggest that elderly and young can increase to the same extent when receiving similar training stimuli.

Estimated Hepatic Blood Flow

When comparing young and elderly individuals on the pharmacokinetics of ICG, the elderly had significantly higher values for half-life of ICG and significantly lower values for the elimination rate constant, K_e. The values of clearance and estimated HBF were not significantly different, although, there was a tendency for the values to be lower for clearance and estimated HBF in the elderly. If the sample had been larger perhaps significance would have been reached.

Studies comparing estimated HBF in the young and elderly have found that older individuals have significantly lower values (Wood et al. 1979; Woodhouse & Wynne, 1988; Wynne et al., 1989; Wynne et al, 1990.). Although these studies claim they have tested healthy elderly adults, no quantitative measurements on health status or fitness levels were given. The subjects in the present study were carefully screened for cardiovascular disease and a number of other conditions (see methods). The subjects were also given a VO_2max test to quantitatively determine fitness levels. The subjects in this study were very healthy and, although sedentary, were able to exercise at high intensities. One of the reasons, therefore, that the elderly subjects in this study may not have had different estimated HBF measurements when compared to younger adults may be due to their health and fitness levels.

The average blood flow for men and women over 65 years of age in the study by Wynne et al. (1989) was 1,211±66 ml/min and 869±62 ml/min (mean±S.E.), respectively. The average blood flow for the subjects under 40 was 1,699±105 ml/min and 1,401±91 ml/min (mean ±S.E) for men and women. In the present study HBF for the men and women over 60 was 1213±178 ml/min and 975±70 ml/min and under 40 was 1460±136 ml /min and 1164±68 ml/min (values are mean ± S.E.), respectively. Another reason that differences may not have been seen in this study is that our values for the younger adults seem to be lower and are closer to those of the elderly than the apparently large differences seen by Wynne et al. (1989). It is hard to compare results since health and fitness status of the subjects in the Wynne et al. (1989) study were not given.

A cross-sectional study by Ducry et al. (1979) comparing HBF in young elite runners and sedentary individuals did not find any differences in estimated HBF between the two groups. The lack of differences in liver function related to physical training may be due to methodological limitations of this study. Subjects were not used as their own controls, instead two independent groups were used. Consequently individual variation might have obscured minor differences due to training. A longitudinal study may have found different results. The study did find the K_e to be somewhat lower for the trained subjects (18.43 ± 2.94) than the untrained (20.5 ± 1.22), although the difference was not significant. Care must be taken in interpreting results from cross-sectional studies due to the confounding factor of genetic differences among subjects.

When subjects were evaluated on the measured parameters of ICG the elderly group showed no changes before and after training. When using ANCOVA to evaluate the young groups, the young exercise group had significant changes in all measured parameters; half-life decreased, elimination rate constant increased, clearance of ICG increased, and estimated HBF increased when compared to the adjusted final means of the control group. When within differences were compared in the young control and training groups significant changes were found in the control group. The control group significantly increased in half-life of ICG, decreased in clearance of ICG, decreased in K_e, and decreased in estimated HBF. On the other hand, the young training group showed only a significant increase in clearance time and a tendency, although not significant, for estimated HBF to increase. Thus, results are more of an effect of what happened to the control group than the training group.

It is difficult to explain why the young control group changed during the 4 month control period and the elderly control group did not change. Cardiac output for the group may have decreased but this was not measured. The resting cardiovascular data did not show changes in resting HR or BP, this indirectly suggests that cardiac output did not decrease unless there was a change in stroke volume without a corresponding change in HR.

The estimated HBF for the young exercise group did have a tendency to be higher. Again, if more subjects were in the study perhaps significance could have been achieved. The slight increase in estimated HBF could be the result of an increase in cardiac output, a reduction in peripheral resistance, or a redistribution of blood. An increase in cardiac output may have occurred since resting HR did not change and exercise training is usually associated with increases in stroke volume. Decreases in peripheral resistance are unlikely since resting BP did not change, although vascular resistance at the level of the liver may have changed. Another possible mechanism that may cause an increase in blood flow to the liver is a redistribution of the blood volume. It has been shown that trained muscles may become more efficient in extracting oxygen from the blood (Ekblom, et al., 1968; Saltin et al., 1968). Clausen et al. (1973) have shown there is a decrease in exercise-induced vasodilation in exercising muscles of trained individuals which allows relatively more blood to the non-exercising muscles and splanchnic-renal areas during exercise than in untrained individuals. In future studies measurements of cardiac output as well as measurements of peripheral blood flow may help explain some of the observed differences seen in estimated HBF.

The elderly and young training groups showed no changes in estimated HBF, although they demonstrated significant improvements in aerobic fitness. This suggests that improvements in VO_2max in young and elderly adults may not necessarily produce corresponding changes in estimated HBF. Whether an exercise program that is longer in duration and/or which elicits a greater increase in VO_2max can produce different results is not known.

Pharmacokinetics of Oral Propranolol

When comparing the young and elderly adults on the pharmacokinetics of oral propranolol there were no significant age-related differences in the area under the curve, time to peak concentration, peak concentration, terminal phase half-life, and the elimination constant. When trying to compare the results from the present study to other studies care must be taken in interpreting the data. Differences in dosage and whether the drug was administered once or given a number of times to reach steady-state will have an effect on how the drug is handled by the body. Health and fitness status of the subjects may also play some role in the pharmacokinetics of the drug. Some studies comparing young and elderly adults have found differences in the pharmacokinetic properties of propranolol (Castleden et al., 1975; Castleden & George, 1979; Vestal, Wood, Branch, Shand, & Wilkinson, 1979; Hitzenberger, Fitscha, Beveridge, Nuesch, & Pacha, 1982; Regardh, 1982). Castleden et al. (1975) were the first to show that higher plasma propranolol concentrations were achieved in elderly compared with young adults after a single 40 mg oral dose. Hitzenberger et al., (1982) found that after giving 80 mg of propranolol 3 times a day for 2 days the elderly individuals had increased AUC, increased peak plasma levels, and decreased elimination rate constants. The study by Vestal et al. (1979) also showed increases in propranolol concentration at steady-state in the elderly.

However, other studies have shown no differences between the young and the elderly (Schneider, Bishop, Yates, Quarterman, & Kendall, 1980; Rigby et al., 1985). Rigby et al., (1985) found no significant differences in clearance, AUC, and terminal phase half-life of propranolol after eight days of treatment with 80 mg/day dosage in young and elderly adults. A study done by Schneider et al., (1980) was designed similar to the present study. Elderly and young subjects were given a single oral dose of 80 mg of propranolol. They found that there were no differences in the concentration-time curves of the two groups, although peak concentrations occurred at different times.

A reason for the different results in the above studies may be not only to the differences in methodology but to the health and fitness levels of the subjects. The subjects of Castleden et al., (1975) were older (78±3) and taken from long stay geriatric wards in which case they may have had concurrent disease. However, in all the above studies there were no quantitative measurements given on parameters of health and fitness. The present study is the only one which carefully screened for underlying disease and quantitatively measured fitness levels. The data in the present study therefore, suggest there are no differences in propranolol concentrations between young and elderly adults. Future studies need to be consistent in their methodology and quantify health and fitness status of their subjects.

After the 4 months of training there were no differences in the measured parameters between the young and elderly subjects in response to training. The elderly exercising group did increase significantly compared to the control group in the time to peak concentration of propranolol. Why this occurred is unknown. The results of the training data suggest that the kinetic parameters of oral propranolol are not affected following 4 months of aerobic training.

Physiological Responses of Oral Propranolol

The design of this study allows for some pharmacodynamic assessment of propranolol but does not allow us to focus in too much detail on the therapeutic effects of a single 80 mg dose of propranolol. To get significant chronic effect on BP and HR a larger or continual dose is needed. However, for descriptive purposes an analyses of BP and HR was performed. The propranolol did not cause significant reductions in BP across time and among the different groups. However, the propranolol did affect the heart rate during the 2 hour period.

Conclusions

Sixteen weeks of endurance training of similar frequency, intensity, duration, mode, and length of program produced similar relative training effects in VO_2max, plasma volume, and blood volume in young (20 to 40 years) and elderly (60 to 80 years) adults. Relative VO_2max increased by 12.5% for the young and by 13.6% for the elderly. Plasma volume increased by 15.2% and blood volume by 12.5% for the young. The elderly increased plasma volume by 12.6 % and blood volume by 9.8%. There were no consistent significant effects of training on resting parameters of HR and BP. The training groups seemed to have lower adjusted mean values for the resting parameters of HR. If more subjects were included in the study perhaps significance would have been reached.

Initial values of estimated HBF were not significantly different between the young and the elderly groups. After the 16 weeks of aerobic training the elderly did not change in parameters of estimated HBF. Adjusted post-training means for the young control (1126 ml/min) and training (1338 ml/min) groups were significantly different. However within group comparisons found the young control group to decrease in estimated HBF while the training group showed a trend to increase.

The initial pharmacokinetic parameters of oral propranolol were not different between the young and elderly groups. After the 16 weeks of aerobic training there were also no changes in the pharmacokinetic parameters of oral propranolol. Only the time of maximal concentration of propranolol was higher in the elderly training group.

Direction for Future Research

The subjects in this study were carefully screened for underlying diseases so the sample of individuals participating in the study were very healthy. In this respect differences in initial values between young and elderly in regards to estimated HBF and pharmacokinetics of oral propranolol were not seen. Therefore differences in these parameters that have been reported may not be a consequence of the aging process but rather a result of underlying disease. Studies are needed that quantify the health and fitness status of individuals when looking at function of the liver.

Endurance exercise in this study did not influence liver function in the elderly. This may be the result of the health and fitness levels of our subjects. Future research needs to examine the effects of exercise training on those individuals who have decreased performance of liver function due to disease or environmental factors. The young control subjects in our study decreased their estimated HBF while the exercise group had a tendency to increase. A reason for the young control group to decrease is unknown. It seems unlikely that cardiac output would have decreased or peripheral resistance increased during the 16 week period. In future studies measurements of cardiac out and stroke volume should be made while HBF is being tested. This would give possible insights to the mechanisms that are involved in the control of HBF.

APPENDIX A
INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

HEALTH CENTER INSTITUTIONAL REVIEW BOARD
D11-22

UNIVERSITY OF FLORIDA • HEALTH SCIENCE CENTER • BOX J-14
VICE PRESIDENT FOR HEALTH AFFAIRS
Gainesville, Florida • zip 32610-0014

December 23, 1991

TO: David T. Lowenthal, M.D., Ph.D., P.O. Box 100277

FROM: B. J. Wilder, M.D., P.O. Box 100014
Chair, Institutional Review Board

Nita W. Davidson, Ph.D.
Vice Chair P.O. Box 100014

SUBJECT: Approval of the Institutional Review Board, Project # 404-91
Title: The Effects of Exercise Training on Hepatic Blood Flow and Propranolol Pharmacokinetics in Normal Elderly Volunteers as Compared to Normal Young Volunteers

The Institutional Review Board (IRB) has recommended the approval of your protocol, identified above, for a period of 12 months, and has determined that human subjects will be at risk.

Approval of your research is, therefore, granted until 12/23/92. By the end of this period you will be asked to inform the Board of the status of your project. If this has not been completed, you must request renewed approval at this time.

You are reminded that changes in the approved research may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects. Where changes have been necessary for the above reasons, these must be promptly reported to the IRB. Also, the principal investigator must report to the Chair of the IRB promptly, and in writing, any unanticipated problems involving risks to the subjects or others such as adverse reactions to biological drugs, radio-isotopes or to medical devices.

If it is anticipated that VA patients will be included in this project, or if the project is to be conducted in part on VA premises or performed by a VA employee during VA-compensated time, final approval should be obtained by application to the Veterans Administration Hospital Research Office.

By copy of this memorandum the chair of your department is reminded that he/she is responsible for being informed concerning research projects involving human subjects in his/her department, and should review the protocols of such investigations as often as he/she thinks necessary to insure that the experiment is being conducted in compliance with our Institution and with DHHS regulations.

cc: B. J. Wilder, M.D.
James E. McGuigan, M.D.
Rhonda Cooper, Pharm.D.
Edward Block, M.D.
Clinical Research Center
DSR

co-PIs: Gregorio J. Guillen, M.D.
Leonard S. Williams, M.D.
✓Michael L. Pollock, Ph.D.
James E. Graves, Ph.D.
Judith Davis, Pharm.D.
Victor A. Convertino, Ph.D.
Joan F. Carroll, M.A.

J. HILLIS MILLER HEALTH CENTER
College of Medicine • College of Nursing • College of Pharmacy • College of Health Related Professions • College of Dentistry
College of Veterinary Medicine • Veterinary Medical Teaching Hospital • Shands Hospital • Veterans Administration Medical Center
EQUAL EMPLOYMENT OPPORTUNITY/AFFIRMATIVE ACTION EMPLOYER

APPENDIX B
DEMOGRAPHIC, MEDICAL, AND ACTIVITY QUESTIONNAIRES

CENTER FOR EXERCISE SCIENCE
UNIVERSITY OF FLORIDA, GAINESVILLE, FL 32611
392-9575

DEMOGRAPHIC INFORMATION

NAME ______________________________ DATE _____/_____/_____
Last First MI Month Day Year

AGE _________ DATE OF BIRTH _____/_____/_____
Month Day Year

SOCIAL SECURITY # _____-_____-_____ PHONE ______________

HEIGHT _______ in. _______ cm

WEIGHT _______ lb. _______ kg

RESIDENCE ____
Street

____
City State ZIP Country

REFERRING PHYSICIAN ________________________________

SURGEON (if applicable)________________________________

HOME PHYSICIAN (if different from referring M.D.) ________________

ADDRESS ____
Street

____
City State ZIP Country

Sex _____ Male
_____ Female

Race _____ White
_____ Black
_____ Asian
_____ Hispanic
_____ Other: _________________

Marital Status

____ Single
____ Married # years ________
____ Divorced or separated # years ________
____ Widowed # years ________

Religion (optional)

____ Catholic
____ Protestant
____ Jewish
____ Jehovah Witness
____ Hindu
____ Muslim
____ None
____ Other: ________

Education Completed

____ 1-8 years
____ 9-12 years
____ 13-16 years
____ 17-18 years
____ more than 18 years
____ High school graduate
____ Bachelor's degree
____ Master's degree
____ Doctoral degree

Occupation (list) ________________________________

Present work status

____ Working full time
____ Working part time
____ Not employed - Reason: ____ Medical ____ Other
____ Retired

Indicate your family income before taxes (U.S. dollar equivalent)

____ less than $10,000
____ $10,000 - $25,000
____ $25,000 - $50,000
____ more than $50,000

STATEMENT OF CONFIDENTIALITY

I understand that information contained on this questionnaire is regarded as confidential, and will not be released without my prior written permission. The information will not be used for the setting of fees. The Center for Exercise Science may, however, use the information for statistical and other research purposes.

________________________________ ____________
Signature Date

CENTER FOR EXERCISE SCIENCE
UNIVERSITY OF FLORIDA, GAINESVILLE, FL 32611
392-9575

CARDIOVASCULAR HISTORY

NAME ____________________________ ID# ___________
DATE ___________

Answer the following questions, indicating the month and year of the event or diagnosis where appropriate.

		Yes	No	Month/Year
1.	Has a doctor ever told you that you have heart disease?	___	___	____/____
2.	Have you ever had a heart attack?	___	___	____/____
3.	Have you ever had chest pain?	___	___	____/____
4.	Have you ever had cardiac catheterization?	___	___	____/____
5.	Have you ever had balloon angioplasty?	___	___	____/____
6.	Have you had coronary artery bypass graft surgery?	___	___	

If yes, list date and number of grafts:

____/____ # grafts: ___ 1 ___ 2 ___ 3 ___ 4+
Mo. Yr.

		Yes	No	Month/Year
7.	Have you ever had a stroke?	___	___	____/____
8.	Do you have hypertension (high blood pressure)?	___	___	____/____

If yes, how long have you had hypertension?

_____ less than 1 year
_____ 1-5 years
_____ 6-10 years
_____ more than 10 years

9. Do you have diabetes mellitus? ____ ____ _____/_____
Yes No Month/Year

10. Do you take insulin for diabetes? ____ ____

If yes, how long have you taken insulin?

_____ less than 1 year
_____ 1-5 years
_____ 6-10 years
_____ more than 10 years

11. Do you take oral hypoglycemics for diabetes? ____ ____

12. Do you have a cardiac pacemaker? ____ ____

If yes, how long have you had a cardiac pacemaker?

_____ less than 1 year
_____ 1-5 years
_____ 6-10 years
_____ more than 10 years

13. Have you had a carotid endarterectomy? ____ ____ _____/_____

14. Has your doctor ever told you that you have a heart valve problem? ____ ____ _____/_____

15. Have you had heart valve replacement surgery? ____ ____ _____/_____

If yes, what heart valves were replaced? ___ mitral ___ aortic

16. Have you had cardiomyopathy? ____ ____ _____/_____

17 Have you had a heart aneurysm? ____ ____ _____/_____

18. Have you had heart failure? ____ ____ _____/_____

19. Have you ever suffered cardiac arrest? ____ ____ _____/_____

20. OTHER MEDICAL PROBLEMS: Indicate if you have had any of the following medical problems:

Past Now
_____ _____ Alcoholism
_____ _____ Allergies
_____ _____ Anemia
_____ _____ Arthritis
_____ _____ Asthma
_____ _____ Back injury or problem
_____ _____ Blood clots
_____ _____ Bronchitis
_____ _____ Cirrhosis
_____ _____ Claudication
_____ _____ Elbow or shoulder problems
_____ _____ Emotional disorder
_____ _____ Eye problems
_____ _____ Gall bladder disease
_____ _____ Glaucoma
_____ _____ Gout
_____ _____ Headaches
_____ _____ Hemorrhoids
_____ _____ Hernia
_____ _____ Hip, knee, or ankle problems
_____ _____ Intestinal disorders
_____ _____ Kidney disease
_____ _____ Liver disease
_____ _____ Lung disease
_____ _____ Mental illness
_____ _____ Neurologic disorder
_____ _____ OB/GYN problems
_____ _____ Obesity/overweight
_____ _____ Phlebitis
_____ _____ Prostate trouble
_____ _____ Rheumatic fever
_____ _____ Seizure disorder
_____ _____ Stomach disease
_____ _____ Thyroid disease
_____ _____ Tumors or cancer - List type: ________________
_____ _____ Ulcers
_____ _____ Other - specify: ________________

21. Surgical Procedures: Indicate if you had had any of the following surgeries, and if so, the appropriate date.

	Yes	No	Month/Year
Adhesion repair	____	____	____/____
Appendectomy	____	____	____/____

21. Surgical Procedures (continued)

	Yes	No	Month/Year
Back surgery	____	____	____/____
Bladder surgery	____	____	____/____
Bowel surgery	____	____	____/____
Breast surgery	____	____	____/____
Cataract surgery	____	____	____/____
Gall bladder surgery	____	____	____/____
Hemorrhoid surgery	____	____	____/____
Joint surgery	____	____	____/____
Kidney surgery	____	____	____/____
Lung surgery	____	____	____/____
OB/GYN surgery	____	____	____/____
Prostate surgery	____	____	____/____
Stomach surgery	____	____	____/____
Other - specify: ______________	____	____	____/____

22. Medications: Indicate the medicines you currently use on a regular basis.

	Yes	No
Allergy medicines/antihistamines	____	____
Antacids	____	____
Antibiotics	____	____
Anti-arrhythmics	____	____
Anti-inflammatory agents	____	____
Aspirin	____	____
Asthma medicines	____	____
Beta blockers	____	____
Birth control pills (# years: ______)	____	____
Blood pressure medicines	____	____
Blood thinners	____	____
Cortisone	____	____
Diabetes medicines/insulin	____	____
Diuretics/"water pills"	____	____
Gout medicines	____	____
Heart medicines	____	____
Hormones/estrogen	____	____
Laxatives	____	____
Nitroglycerin	____	____
Pain medicines	____	____
Psychiatric medicines/anti-depressants	____	____
Sedatives/sleeping pills	____	____
Seizure medicines	____	____
Thyroid medicines	____	____
Tranquilizers	____	____
Vitamins/iron	____	____
Other - specify: ________________		

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392-9575

FAMILY HEALTH HISTORY

NAME ______________________________ ID# ____________
DATE ____________

A. If any members of you immediate family have or have had any of the following conditions, indicate their age at the time of the event:

	Father	Mother	Brother(s)	Sister(s)
Heart Attack	______yr	______yr	______yr	______yr
Stroke	______yr	______yr	______yr	______yr
Coronary Artery Disease	______yr	______yr	______yr	______yr
If deceased, not age at time of death	______yr	______yr	______yr	______yr

B. Indicate if any members of you immediate family have or have had the following conditions by marking the appropriate lines:

	Father	Mother	Brother(s)	Sister(s)
High Blood Pressure	______yr	______yr	______yr	______yr
High Cholesterol	______yr	______yr	______yr	______yr
Diabetes	______yr	______yr	______yr	______yr
Obesity	______yr	______yr	______yr	______yr

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ACTIVITY STATUS

NAME ______________________ ID# __________
DATE __________

1. Please indicate your usual activities.

	Frequency per month					Minutes per session			
	1-4	5-8	9-12	13-16	17^{+}	0-20	20-40	40-60	60^{+}
__ Badminton	__	__	__	__	__	__	__	__	__
__ Baseball/softball	__	__	__	__	__	__	__	__	__
__ Boating	__	__	__	__	__	__	__	__	__
__ Bowling	__	__	__	__	__	__	__	__	__
__ Cycling (motor)	__	__	__	__	__	__	__	__	__
__ Cycling (road)	__	__	__	__	__	__	__	__	__
__ Cycling (stationary)	__	__	__	__	__	__	__	__	__
__ Dancing (aerobic)	__	__	__	__	__	__	__	__	__
__ Golf (ride)	__	__	__	__	__	__	__	__	__
__ Gold (walk)	__	__	__	__	__	__	__	__	__
__ Gymnastics	__	__	__	__	__	__	__	__	__
__ Hiking	__	__	__	__	__	__	__	__	__
__ Horseback riding	__	__	__	__	__	__	__	__	__
__ Hunting/fishing	__	__	__	__	__	__	__	__	__
__ Jogging/running	__	__	__	__	__	__	__	__	__
__ Martial arts	__	__	__	__	__	__	__	__	__
__ Racquetball	__	__	__	__	__	__	__	__	__
__ Handball	__	__	__	__	__	__	__	__	__
__ Rope jumping	__	__	__	__	__	__	__	__	__
__ Rowing, canoeing	__	__	__	__	__	__	__	__	__
__ Sailing	__	__	__	__	__	__	__	__	__
__ Skating	__	__	__	__	__	__	__	__	__
__ Skiing (x-country)	__	__	__	__	__	__	__	__	__
__ Skiing (downhill)	__	__	__	__	__	__	__	__	__
__ Skiing (water)	__	__	__	__	__	__	__	__	__
__ Soccer/football	__	__	__	__	__	__	__	__	__
__ Swimming	__	__	__	__	__	__	__	__	__
__ Table tennis	__	__	__	__	__	__	__	__	__
__ Tennis	__	__	__	__	__	__	__	__	__
__ Volleyball	__	__	__	__	__	__	__	__	__
__ Walking	__	__	__	__	__	__	__	__	__
__ Weight training	__	__	__	__	__	__	__	__	__
__ Yardwork/gardening	__	__	__	__	__	__	__	__	__

__ Other - specify: ____

2. Does you usual job require sustained physical activity?
____ Yes ____ No ____ Not employed ____ Not applicable (retired)

3. How would you rate your physical fitness (endurance)?

low			medium			high
1	2	3	4	5	6	7

4. How would you rate your strength?

low			medium			high
1	2	3	4	5	6	7

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UNIVERSITY OF FLORIDA, GAINESVILLE, FL 32611
392-9575

TOBACCO HISTORY

NAME ______________________________ ID# ____________
DATE ____________

1. Have you ever used any tobacco product on a regular basis?
_____ Yes
_____ No

IF YES: Continue
If NO: Stop here

2. What form(s) of tobacco do/did you regularly use?

Past	Now		# years	Amount/Day	
____	____	Cigarettes	________	_______	packs
____	____	Cigars	________	_______	cigars
____	____	Pipe	________	_______	pipefuls
____	____	Chewing tobacco	________	_______	chaws
____	____	Snuff	________	_______	dips

3. Are you a former smoker?
_____ Yes
_____ No

IF YES:

a. How long ago did you stop smoking?

_____ Less than 6 months
_____ 6-12 months
_____ 1-2 years
_____ 3-5 years
_____ 5-10 years
_____ more than 10 years

b. What was your reason for stopping?

_____ Doctor's advice
_____ Concern about health
_____ Heart surgery or cardiac event
_____ Family pressure
_____ Education program
______ Other - specify: ____________________________

APPENDIX C
INFORMED CONSENT TO PARTICIPATE IN RESEARCH

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

J. HILLIS MILLER HEALTH CENTER VA MEDICAL
CENTER
UNIVERSITY OF FLORIDA GAINESVILLE, FL
32602
GAINESVILLE, FL 32610

You are being asked to volunteer as a participant in a research study. This form is designed to provide you with information about this study and to answer any of your questions.

1. TITLE OF RESEARCH STUDY

THE EFFECTS OF EXERCISE TRAINING ON HEPATIC BLOOD FLOW AND PROPRANOLOL PHARMACOKINETICS IN NORMAL ELDERLY VOLUNTEERS AS COMPARED TO NORMAL YOUNG VOLUNTEERS

2. PROJECT DIRECTOR

Name:	David T. Lowenthal, M.D., Ph.D.
Telephone Number:	(904) 374-6077

3. THE PURPOSE OF THE RESEARCH

The purpose of this research study is to learn whether 16 weeks of exercise will change the blood flow to your liver and whether a heart and blood pressure medicine, propranolol (Inderal) will be eliminated from your body faster or slower as a result of the exercise.

4. PROCEDURES FOR THIS RESEARCH

This study will last about 18 weeks. On the first visit, there will be an orientation program at the Center for Exercise Science where this study will be conducted in order to familiarize you with the Center and staff. At this time, you will be able to ask questions and obtain further information about all the aspects of the study. Also on this visit you will receive a history, physical examination and laboratory studies will be done to evaluate your blood count, liver function, kidney function and cholesterol. You will also have an electrocardiogram (EKG) done at this time. For the blood tests, approximately three teaspoons (approximately 15 ml) of venous blood will be drawn. There will be a nominal fee of $45.75 for the blood analyses. At the end of the exercise training period for the study, the physical exam and EKG will be repeated.

On the second visit, you will have a plasma (the liquid portion of your blood that is circulating in your body) volume determination. In order to do this, a small intravenous (IV) catheter will be put in a small vien in each of your forearms. A sample of blood (1/2 teaspoonful or 2.5 ml) will be drawn through one IV. Then through the other IV you will be given an injection of Evans blue dye which is the substance used during plasma volume determination. After that injection, another 1/2 tablespoon of blood will be drawn through the IV. In this manner, you will not have to be stuck by a needle each time as the blood can be simply drawn through the IV. Following this, you will take an exercise test on a treadmill while your electrocardiogram and blood pressure are being monitored. Every two minutes during this test, the exercise will become more difficult, until the physician stops the test because of certain signs or symptoms, or when you are unable to continue because of fatigue. If you have no cardiovascular or other significant medical abnormalities considered a reason for you not to undergo exercise training, you will be included in the study.

At the third visit, the exercise test on a treadmill will be repeated but during this test you will be breathing through a special mouthpiece so that the amount of oxygen that you consume during this test can be measured. This will be a measurement of your actual physical fitness.

The fourth and last visit prior to assignment to the control or exercise group will consist of the hepatic blood flow measurement and the clearance of propranolol. The hepatic blood flow will be measured in a manner similar to the plasma volume determination. The only difference is that indocyanine green dye will be used instead of Evans blue, and 1/2 tablespoon blood samples will be drawn through the IV every three minutes for one half hour. For the clearance of propranolol you will be given, by mouth, an 80 mg pill to take. Every hour for a ten hour period, we will draw slightly less than a half teaspoon of blood (2 ml) through the IV in place. This will conclude the first period of the study.

The second period of this study will be the exercise training period which will go on for sixteen weeks. You will be randomly assigned (much like the flip of a coin) to undergo this sixteen week period of exercise training or to receive no training and to carry out your normal routine of daily life. If you are randomized to the training group, you will undergo a gradual program of exercise training three times per week for a sixteen week period. These training sessions will be done under the supervision of staff trained in exercise prescription and exercise training. Each training session will consist of walking on a treadmill. Gradually over the sixteen week period, the incline of the treadmill and the speed of the treadmill as well as the time you spend on the treadmill will be slowly increased according to your ability to increase exercise training. If you do not participate in the actual exercise training program, you will be counseled on maintaining your normal life style until the completion of the research project. This group of people will be the control group of the study.

After the sixteen week exercise training period, there will be the post-exercise training testing period, which will be completed within one week. On the first visit, once again the physical examination, plasma volume determination and the exercise stress test with the mouthpiece in order to measure oxygen consumption will be done.

At the second visit, once again, the determination of hepatic blood flow, and the clearance of propranolol will be performed as was done in the fourth visit of the initial screening and testing period.

5. POTENTIAL RISKS OR DISCOMFORTS

If your wish to discuss these or any other discomforts you may experience, you may call the Project Director listed in #2 of this Form.

Endurance exercise testing (GXT) and training is associated with a small risk of cardiovascular complications. The risk for exercise testing is about three to four non-fatal incidents (events) in 10,000 GXT's and one fatal event per 25,000 tests. The risk will be minimized in this study because all the personnel involved with testing and training are experienced in working with older men and women. In addition, a physician will monitor all the exercise tests and your blood pressure, heart rate and EKG will be closely monitored during the exercise tests. You can expect some fatigue and breathlessness to accompany the exercise testing at the start, the middle and the end of the study. In regard to exercise training, only one fatal event has occurred over the past fifteen years of exercise training at the Aerobics Activity Center in Dallas. Their event rate is less than one in over one millions miles of walking and jogging. Thus, the risk of serious injury is considered extremely low for exercise testing and training. In this study, your heart rate and level of exertion will be monitored frequently as you exercise in order to further assure your safety. However, there is the possibility of minor injury, pulling a muscle or twisting an ankle or knee during the exercise training phase of the study.

The risks of drawing blood from a vein and the placement of the IV catheters include discomfort at the sit of the needle placement, possible bruising and swelling around the site of needle placement, rarely an infection and uncommonly, faintness from the procedure. The risk is minimized by the use of sterile techniques and infusion of sterile saline to keep the catheter open during the duration of the placement. The risk of serious injury with blood drawing and catheterization is, therefore, quite minimal.

The risks involved in the intravenous injection of indocyanine green in order to measure your hepatic blood flow is minimal. There has never been reported a serious event from this type of rapid injection.

In regard to the plasma volume determination, the risks involved are the same for the indocyanine green infusion.

The risks involved with propranolol are related to taking a one time dose of propranolol 80 mg by mouth. This drug is rarely associated with a rash-type of allergic reaction, and the possible side effects of this one time dose could be a slowing or the heart rate or a lowering of your blood pressure. However, patients who participate in this study will be screened very carefully to make sure they do not have a pre-existing condition which would put them at risk for some other type of adverse reaction to propranolol. A physician will be present during this test.

The total amount of blood which will be drawn throughout the entire study is slightly more than one half of a unit of blood donated (approximately 165 ml of blood for the entire study).

The financial risk for you during this study will be the one time lab fee of $45.75 for the blood tests at the initial visit of the study.

6. POTENTIAL BENEFITS TO YOU OR TO OTHERS

You will receive a complete cardiovascular examination and a battery of tests at the start of the study. The results of the studies will be available to your private physician. You will also receive an individualized prescription based on your exercise capacity and the chance to complete a sixteen week training program at no charge and under the close supervision of a highly qualified research team. In general we will all learn whether exercise training in older people will alter the flow of blood to the liver and whether or not this will have important consequences for the clearance of various drugs from the body by the liver.

7. ALTERNATIVE TREATMENT OR PROCEDURES, IF APPLICABLE

You have the alternative of not participating in the study.

8. GENERAL CONDITIONS

I understand that I will___ /will not _X_ receive money for my participation in this study. If I am compensated, I will receive____________________________

____

I understand that I will___/will not___ be charged additional expenses for my participation in this study. If I am charged additional expenses these will consist of ______blood count and blood chemistry screening__________ ______.

I understand that I am free to withdraw my / my child's consent and discontinue participation in this research project at any time without this decision affecting my / my child's medical care. If you have any questions regarding your rights as a subject, you may phone 392-3063.

In the event of my / my child's sustaining a physical injury which is proximately caused by this experiment, ______professional medical______ care received at the J. Hillis Miller Health Center exclusive of hospital expenses will be provided me without charge. This exclusion of hospital expenses does not apply to patients at the Veterans Administration Medical Center (VAMC) who sustain physical injury during participation in VAMC-approved studies. It is understood that no form of compensation exists other than those described above.

I also understand that the University of Florida and the Veterans Administration Medical Center will protect the confidentiality of my records to the extent provided by Law. The Study Sponsor, Food and Drug Administration or either Institutional Review Board may ask to review my records, however the records will remain confidential as only a number and initial will be used.

9. SIGNATURES

I have fully explained to ______________________________
the nature and purpose of the above-described procedure and the benefits and risks that are involved in its performance. I have answered and will answer all questions to the best of my ability. I may be contacted at telephone number ______________________.

Signature of Principal or Co-Principal Investigator Obtaining Consent — Date

I have been fully informed of the above-described procedure with its possible benefits and risks and I have received a copy of this description. I have given permission of my / my child's participation in this study.

Signature of Patient or Subject or Relative or Parent or Guardian (specify) — Date

Signature of Child (7 to 17 years of age) — Date

Signature of Witness — Date

APPENDIX D
INSTRUCTIONS FOR TESTING DAYS

To confirm or change appointment: Call 392-9575 and ask for Linda Garzarella or Lynn Panton.

Visit 2:
PHYSICAL EXAM, BLOOD CHEMISTRY SCREENING, AND DIAGNOSTIC EXERCISE TEST (2 hours)

WHEN:

Month ____________________

Day ____________________

Time ____________________

WHAT: During this visit you will need to return your completed medical history questionnaire. The medical history questionnaire will be reviewed and a physical examination will be given by a physician. After the examination a small blood sample will be drawn for a blood chemistry and lipid profile. You will then walk on a treadmill while your blood pressure and EKG are continuously monitored by a physician.

WHERE:

The Center for Exercise Science
In the basement of the Florida Gymnasium

YOUR INSTRUCTIONS:

1) No meals, coffee, tea, or other beverages that contain caffeine 12 hours prior.
2) Wear a short sleeved shirt, T-shirt, or sleeveless shirt, comfortable shoes, and shorts or comfortable slacks. Ladies please do not wear body leotards or pantyhose.
3) No exercise 24 hours prior.
4) Take medications as you normally would.
5) Bring a snack to eat after tests are completed.

To confirm or change appointment: Call 392-9575 and ask for Linda Gazarella or Lynn Panton.

Visit 3:
BLOOD PRESSURE, BODY COMPOSITION, PLASMA VOLUME, AND PRACTICE SESSION (2 HOURS)

WHEN: Month____________________

Day ____________________

Time ____________________

WHAT: This visit will begin with resting blood pressure measurements.

The next procedure will be the measurement of blood volume, which will involve the injection of a special dye, and the collection of a blood sample 10 minutes later.

The next procedure will be the measurement of your amount of body fat which will be determined by skinfold pinches. This technique will measure the fat deposits beneath the skin at several sites on your body.

Finally you will be familiarized with walking on the treadmill while wearing a headgear and breathing through a mouthpiece.

WHERE: The Center for Exercise Science
In the basement of the Florida Gymnasium

YOUR INSTRUCTIONS:

1) No meals, coffee, tea, or other beverages that contain caffeine, for 3 hours prior to testing.
2) Men wear shorts and short-sleeved shirt.
3) Women wear two-piece swim suit or shorts and halter top or shorts and brassier. No pantyhose or leotards please.
4) No exercise 24 hours prior.
5) Take medication as you normally would.

To confirm or change appointment: Call 392-9575 and ask for Linda Garzarella or Lynn Panton.

Visit 4:
BLOOD PRESSURE MEASUREMENT AND MAXIMUM TREADMILL EXERCISE TEST (2 hours)

WHEN: Month ____________________

Day ____________________

Time ____________________

WHAT: This visit will again begin with resting blood pressure measurements followed by walking on the treadmill. As before your EKG and blood pressure will be continuously monitored during the test. You will be asked to give your best effort so that we can accurately measure your fitness level before the training starts. You will wear the headgear from your earlier practice session.

WHERE: The Center for Exercise Science
In the basement of the Florida Gymnasium

YOUR INSTRUCTIONS:

1) You may have a light meal 3 hours prior.
2) No coffee, tea, or other beverages that contain caffeine, 3 hours prior.
3) Wear a short sleeved shirt, T-shirt, or sleeveless shirt, comfortable shoes, and shorts or comfortable slacks. Ladies please do not wear body leotards or pantyhose.
4) No exercise 24 hours prior.
5) Take medications as you normally would.

To confirm or change appointment: Call 392-9575 and ask for Linda Garzarella or Lynn Panton.

Visit 5:
HEPATIC BLOOD FLOW DETERMINATION AND PROPRANOLOL CLEARANCE (11 hours)

WHEN:

Month ____________________

Day ____________________

Time ____________________

WHAT: During this visit hepatic blood flow will be determined.This will involve the injection of a special dye and the collection of blood every 3 min for 30 minutes. The next procedure will be the measurement of Propranolol clearance. Propranolol will be given orally and blood will be drawn at hour intervals for 10 hours.

WHERE: The Clinical Research Center (CRC)
Located on the third floor of Shands Hospital (See Map)

YOUR INSTRUCTIONS:

1) No meals, coffee, tea, or other beverages that contain caffeine 12 hours prior.
2) No exercise 24 hours prior.
3) Take medications as you normally would.
4) This is a relatively long procedure so please bring food or snacks to eat while you are waiting.
5) Feel free to bring reading material, sewing, or work.

APPENDIX E
24 HOUR HISTORY QUESTIONNAIRE

CENTER FOR EXERCISE SCIENCE
UNIVERSITY OF FLORIDA, GAINESVILLE, FL 32611
392-9575

24-HOUR HISTORY QUESTIONNAIRE

NAME: ______________________________ DATE __________
TIME __________

How much sleep did you get last night? (Please circle one)
1 2 3 4 5 6 7 8 9 10 (Hours)

How much sleep do you normally get? (Please circle one)
1 2 3 4 5 6 7 8 9 10 (Hours)

How long has it been since your last meal or snack? (Please circle one)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 (Hours)

List the items below:

____

When did you last have:
A cup of coffee or tea ____________________
Smoke a cigarette, cigar, or pipe ____________________
Drugs (including aspirin) ____________________
Alcohol ____________________
Last time given blood ____________________
Any recent illnesses ____________________
Suffer from respiratory problem ____________________
What sort of physical exercise did you perform yesterday? __________

____

What sort of physical exercise have you performed today? __________

____

Describe your general feelings by checking one of the following:

__________ Excellent
__________ Very, very good
__________ Very good
__________ Good
__________ Neither good or bad

__________ Bad
__________ Very bad
__________ Very, very bad
__________ Terrible

APPENDIX F
DATA COLLECTION FORMS FOR ESTIMATED HEPATIC BLOOD FLOW AND ORAL PROPRANOLOL

University of Florida
Center for Exercise Science
Gainesville, FL 32611

ICG Lot #________

Hepatic Blood Flow and Propranolol Clearance Study: ICG and Propranolol Blood Draws (Total Blood Drawn: 104ml)

Name ______________________ Date ________ Subject # ________

Wt (kg) ________ x 0.5 mg/kg = ________ mg ICG ÷ 5 mg/ml = ________ ml ICG

Baseline Blood 12ml blood (12 ml blood) Time: ________

1) ICG (2ml plasma)
2) Propranolol (2 ml plasma)
3) a-1 GlycoProtein (3 ml plasma)

Indocyanine Green 4ml blood/draw (40 ml blood) Time: ________

Tube #	Time (min)	HR	BP	Comments
Baseline	00:00			
1	03:00			
2	06:00			
3	09:00			
4	12:00			
5	15:00			
6	18:00			
7	21:00			
8	24:00			
9	27:00			
10	30:00			

Propranolol 5ml blood/draw (52 ml blood) Time: ________
except 12ml at 02:00 (Protein Binding)

Tube #	Time (hr)	HR	BP	Comments
1	00:30			
2	01:00			
3	01:30			
4	**02:00**			
5	03:00			
6	04:00			
7	06:00			
8	08:00			
9	10:00			

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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